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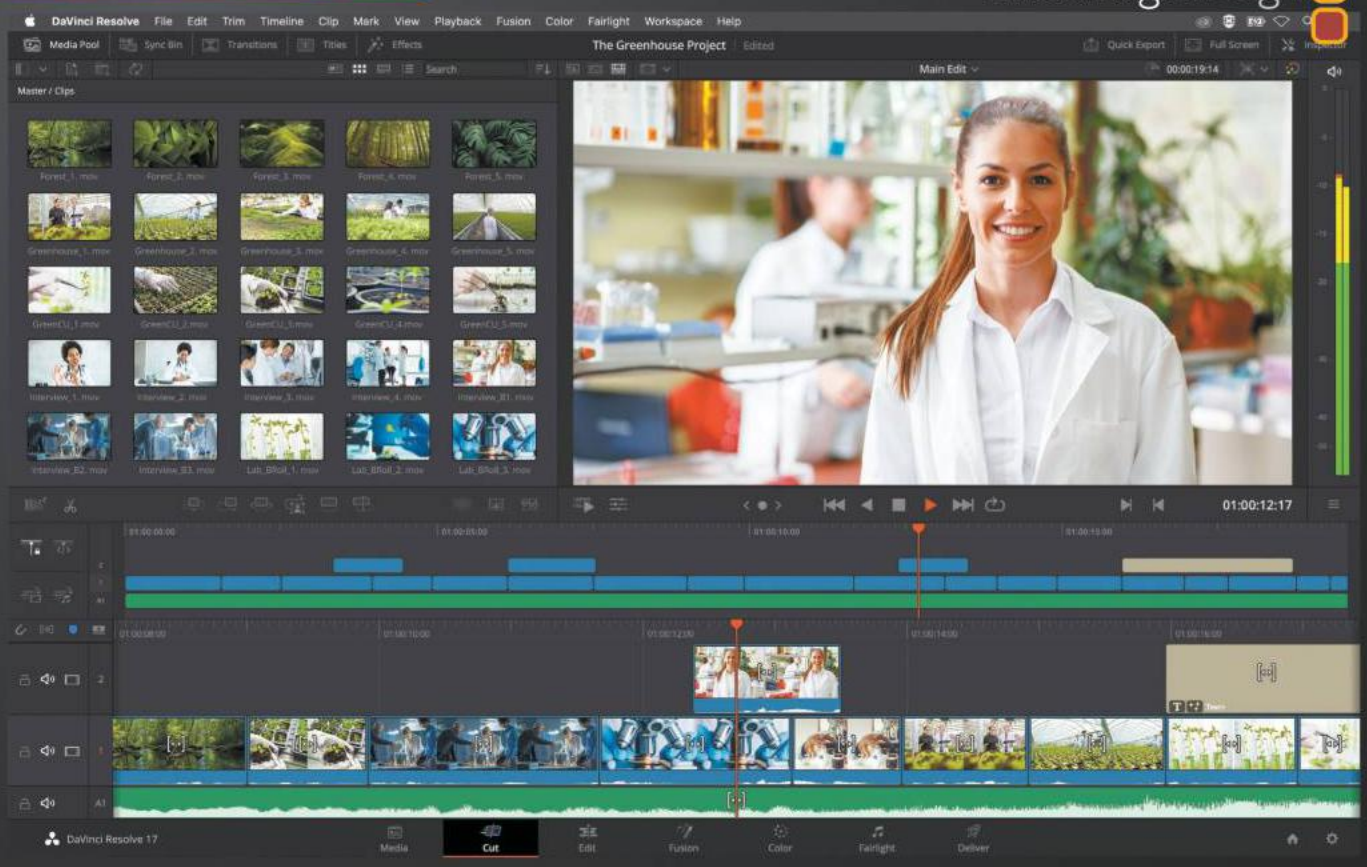

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ON THE COVER
As Earth warms, additional water evaporates into the air. Warmer air, in turn, can hold more of that vapor. A juicier atmosphere provides extra energy and moisture for destructive rainstorms and helps tropical storms like Hurricane Ida intensify faster, leaving precious little time to warn people in the crosshairs.
Illustration by Mark Ross.

Photograph by Thoko Chikondi

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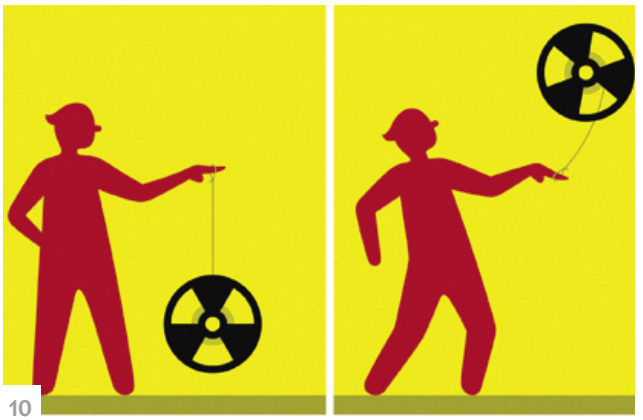

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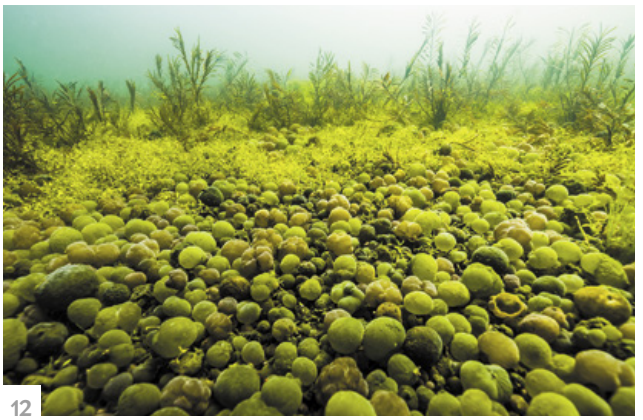

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Laura Helmuth is editor in chief of *Scientific American*.
Follow her on Twitter @laurahelmuth

Wisdom Deified

If you look across cultures and through history, there's a deity for pretty much anything. The sun, ocean, harvest, lightning, love, poetry, all the good stuff. For some of us at *Scientific American,* our favorite is the ancient Egyptians' Thoth, god of science, knowledge, wisdom and writing. Thoth is often depicted as a baboon—making him the only god in the pantheon whose animal representative was not native to Egypt. Egyptologists have wondered where, exactly, the mummified baboons buried with pharaohs came from and why a certain species was considered sacred. Now primatologist Nathaniel J. Dominy discusses (*page 46*) how the behaviors of *Papio hamadryas* fit into ancient Egyptian theology and how isotope analysis of these baboons points to the location of the lost kingdom of Punt. It's a delightful story that may make you want to hoot at the rising sun.

In our cover story this month (*page 26*), climate scientist Jennifer A. Francis shows how water vapor—an underappreciated greenhouse gas—is causing disastrous floods and extreme weather around the world. Vapor storms are dumping more rain more quickly, energizing thunderstorms and hurricanes, and making summer days and nights more dangerously humid. Francis, who is a member of *Scientific American*'s advisory board, calls for better instrumentation to measure temperatures below the sea surface, which should improve forecasts of hurricane strength and rainfall. (For the opposite end of extreme weather caused by the climate emergency, see page 74 for our Graphic Science piece on extreme droughts.)

The James Webb Space Telescope is finally—we hope!—going into space this year. It was initially scheduled to launch in 2007 but was pushed back by problems with the contractor, budget overruns, human error and the general complications of creating a spaceship with a tennis-court-size sun shield that will orbit 1.5 million kilometers from Earth. NASA photographer Chris Gunn has been capturing the painstaking progress of the mission as JWST was being built and tested, and seeing his gorgeous pictures with text from senior editor Clara Moskowitz on page 54 is a great way to anticipate liftoff in December (again, we hope).

In another hopeful story, sustainable food expert Raj Patel takes us on a tour of communities that are turning to agroecology, a practice that integrates social science, ecology, soil health, community building, and more into traditional agricultural science. The United Nations hosted a summit on food systems in September that excluded agroecology, and Patel makes a strong case that current practices are not sustainable and that agroecology is necessary to end world hunger (*page 34*).

The idea of editing genes to repair genetic diseases has seemed promising for decades, but the approach failed when several young people died in clinical trials. On a personal note, the day the news broke in 2003 that an experimental treatment for severe combined immunodeficiency (SCID, or "bubble boy disease") had caused leukemia in some of the children, a group of science writers in Washington, D.C., attended a previously scheduled happy hour, and it was the glummest happy hour ever. Many of us were covering the trial and were devastated that it had failed. Now researchers have figured out how to deliver gene therapy more safely and for more types of diseases, including cancer. Our special Innovations In report, starting on page S1, explains how the field has matured, what the successes are so far, and how to manage hope and hype when people are desperate for cures. SA

Illustration by Nick Higgins

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July 2021

"Science is not really about 'right,' 'wrong,' 'true' or 'false.' Theories should be evaluated as more or less 'useful within a certain context.'"

GEOFF DAVIES *AUSTRALIAN NATIONAL UNIVERSITY*

SEQUESTERING CO_2 IN ROCKS

"The Carbon Rocks of Oman," by Douglas Fox, described efforts by geologist Peter Kelemen and other scientists to potentially sequester carbon dioxide in mantle rock formations. As a physical chemist who picked up the rudiments of geology and geochemistry during environmental investigations, I was intrigued by the article, which discussed various mechanisms that might be used to enhance the process or lower costs, including both in situ and ex situ concepts.

Would it be possible to use standard petroleum methods such as fracking with high-pressure liquids to improve the permeability of the mantle rocks? And would seawater—which would already be used to sequester CO_2 in Kelemen's plan—be a candidate for such fracking?

Finally, do the calcium and magnesium in seawater also react with CO_2, especially at the higher pressures and temperatures at depth? And if so, might this tend to "plug up" the veins, natural or induced, before the solution could migrate very far?

GARY MCKOWN *West Chester, Pa.*

Fox describes a natural process that permanently petrifies CO_2 as magnesium carbonate ($MgCO_3$) or calcite ($CaCO_3$) in mantle rock in Oman.

Each CO_2 molecule has two oxygen atoms, whereas there are three in each molecule of $MgCO_3$ or $CaCO_3$. If the described process was greatly intensified to rid the atmosphere of CO_2, is there a possibility that we would permanently "lose" too much oxygen? Would we exchange one evil for another?

URSULA GARTENMANN *Zurich*

FOX REPLIES: In response to McKown's letter: Injection of CO_2 could indeed potentially be enhanced with artificial fracking using seawater. Pressurized "supercritical" CO_2 could also be a possible fracking fluid.

The calcium and magnesium naturally present in seawater should not increase the tendency of pores in the rock to be clogged with precipitating carbonates. This is because fluids in the water underground already contain calcium and magnesium. The natural carbonation reactions actually involve an initial step in which these elements in the rock dissolve in the CO_2-rich water (which is acidic). Ions of calcium and magnesium then react with the CO_2 and precipitate back into solid minerals.

Gartenmann asks an interesting question. Fortunately, the reactions that convert CO_2 into CO_3 do not consume oxygen gas (O_2). Instead they consume oxygen atoms that are already present in the water and in minerals such as olivines (including Mg_2SiO_4 and Fe_2SiO_4), serpentine [$Mg_3Si_2O_5(OH)_4$] and brucite [$Mg(OH)_2$]. Because of the oxygen contents of such minerals, very roughly, Earth's crust and mantle contain more than a million times more oxygen than the atmosphere!

But even if we were to assume that all of the extra oxygen atoms needed to sequester carbon in rock came from the air, we would lose only a minuscule amount of them: mineralizing a billion metric tons of CO_2 would consume about 0.00003 percent of the estimated 1.2 quadrillion metric tons of O_2 in Earth's atmosphere. And mineralizing a trillion metric tons of CO_2 would consume only about 0.03 percent of that oxygen.

SCIENCE AND "TRUTH"

In "Is Science Actually 'Right'?" [Observatory], Naomi Oreskes argues that it offers a process of discovery rather than providing absolute truth.

Science is not really about "right," "wrong," "true" or "false." My work studying Earth's interior, where observations are always incomplete and often not very accurate, has led me to the idea that theories should be evaluated as more or less "useful within a certain context." I find this avoids much confusion about what science provides.

For example, Isaac Newton's theory of gravity was superseded by Albert Einstein's, but that did not make Newton's theory "wrong" or make Einstein's "right." Newton's theory is still extremely useful in many contexts. Einstein's theory is useful in a much broader range of them: it can do a better job of explaining Mercury's orbit and black holes. If someday a better idea than Einstein's general theory of relativity comes along, or observations are found that are inconsistent with that theory, then Einstein will not have been "wrong" either.

A physician with a good scientific background will probably be more useful to your health than a typical politician, however prominent. And a climate scientist's projections into the future are likely to be more useful than those of an ill-informed coal executive. On the other hand, your average shopkeeper may have a better understanding of economies than most neoclassical economists, whose theories bear no useful resemblance to observable economies.

GEOFF DAVIES *retired senior fellow, Australian National University*

BETTER GUN SAFETY

In "Patient Care Must Include a Gun Talk" [Forum], Chethan Sathya and Sandeep Kapoor argue that doctors should talk to their patients about firearm safety. Doctors are well equipped for good discussions with their patients about exercise, smoking, drug and alcohol consumption, and diet as they relate to health. But few of them, including my doctors, own firearms, and most know little about appropriate firearm safety courses.

I own a firearm and have taken in-person safety courses, which have been invaluable. Doctors would be more effective and trustworthy on this subject if they were better informed about safe gun ownership resources, including local safety courses. For those millions of citizens who are going to own firearms, nothing improves gun safety practices better than a well-taught training course.

ANDREW GOLDSTEIN *Portland, Ore.*

NEW ERA OF PROTEINS

Your July issue was outstanding. I have never enjoyed reading so many of the articles in any one edition of *Scientific American*. All of them had important information.

I especially liked "Life, New and Improved," Rowan Jacobsen's feature on the creation of artificial proteins and the use of the technology in the development of a new COVID vaccine. I've recommended it to my four granddaughters as must reading. One is a research biologist doing work in neuroscience. Two just completed their sophomore years in different colleges, and the fourth will be a senior in high school next year.

J. P. UTTLEY *via e-mail*

This is, without a doubt, the most intriguing article I have read in this magazine, and I am a long-time subscriber. I'm looking forward to follow-ups because this is obviously the dawn of a new era. I hate the overuse of hyperbolic descriptions, but the superlative fits well here.

STUART TAYLOR *Perth, Australia*

ERRATUM

"Switchgrass Cleaner," by Susan Cosier [Advances; August 2021], should have described other researchers using plants to clean up "PCBs," not "PDBs."

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States vs. Health

Bad new state laws make it hard for public health agencies to stop disease

By the Editors

The happiest place on Earth got seriously ill in 2015. A large outbreak of measles started in Disneyland in California, and the highly contagious and often deadly disease ultimately spread to 307 people across North America. It was only stopped after public health agencies traced thousands of potentially infected people and isolated the sick ones, quashing the epidemic.

Local health agencies protected lives early this year in Oregon, when an outbreak of Legionnaires' disease in Multnomah County hospitalized four and killed one. Health department workers went door to door, notifying 100 people that their building's water was contaminated with disease-causing bacteria. The workers helped them relocate and provided safe meals.

During the COVID pandemic, public health officials protected people by requiring masking and physical distancing. In 2020, for instance, Kansas counties that adopted mask mandates, aided by health departments, had significantly fewer hospitalizations, deaths and cases than did counties that rejected masks.

But now politicians in many states are trying to prevent this kind of lifesaving work. They are passing laws that take control of public health and safety measures away from local agencies and put it in the hands of state legislatures, which have no medical expertise. In recent months at least 15 states have enacted or are considering laws that severely limit the authority of county and city agencies to close dangerous facilities or isolate people infected with deadly and contagious illnesses such as measles or COVID, as well as other public safety actions. Hundreds of similar bills are under development, according to a report from the Network For Public Health Law and the National Association of County and City Health Officials.

"It's equivalent to taking away the ability of doctors to write prescriptions," says Georges Benjamin, executive director of the American Public Health Association. "These are proven public health strategies going back hundreds of years." The bills and laws prevent local authorities from responding quickly to local conditions, which is dangerous because things change fast during a disease outbreak and different threats require different responses.

Many of the bills appear fueled by the misplaced anger of Republican lawmakers at health measures taken to contain the pandemic, including activity restrictions and business closures or occupancy limits. Some examples of new legislation are:

- Ohio passed a law giving the state legislature the power to void "any order or rule for preventing the spread of contagious or infectious disease" from the governor or the state health department. The law also restricts the ability of local health agencies to issue isolation and quarantine orders and allows the state to override local decisions.
- Kansas approved legislation that designates local politicians, such as county commissioners, as the local health authority, and says that health boards cannot issue many types of orders unless those politicians grant approval. The law also limits contact tracing, an essential public health tool to find people exposed to dangerous diseases, as it did during the Disneyland outbreak.
- Florida enacted a law that automatically ends emergency health orders after seven days and requires a majority vote by local government officials to extend them. It gives the legislature unilateral power to terminate orders issued by the governor during a state of emergency.
- Montana passed legislation that prohibits local health orders that limit physical attendance at houses of worship.

It is true that health orders such as quarantines restrict individual freedom. But agencies cannot impose such measures arbitrarily, says Benjamin, and they are subject to quick review by courts. Health officials have had tremendous success in preventing the spread of illness and saving lives by customizing fast responses to different diseases. A salmonella outbreak at a restaurant calls for different measures than a hepatitis outbreak in a homeless population, or a person with tuberculosis who has been traveling around a county, or a bacteria-contaminated city water supply. Limits such as an automatic seven-day cutoff will prevent the most effective reactions and lead to illness and death.

The politicians who voted to hobble health are up for election, both this year and next. Voters can rescind these harmful actions by voting them out of office and supporting candidates who will protect health and well-being. Legislators have the right to review laws and change them. They do not have the right to practice medicine. SA

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Illustration by Martin Gee

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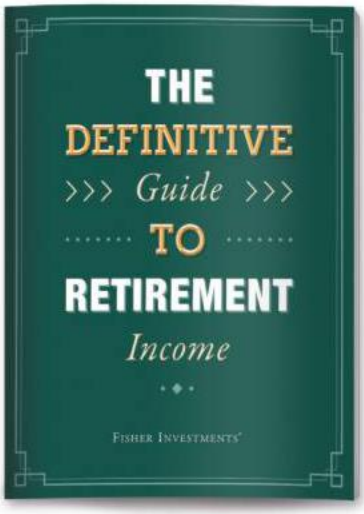

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Next-Gen Nuclear Reactor Hype

There is little evidence fanciful new designs will be cheaper or safer

By Elliott Negin

The U.S. nuclear power industry is at an impasse. Since 2012, 11 of the 104 light-water reactors in operation at the time have closed, mainly as a result of aging infrastructure and the inability to compete with natural gas, wind and solar, which are now the cheapest sources of electricity in the U.S. and most other countries worldwide.

One way the industry is trying to reverse the trend is by looking to what it likes to call "advanced" reactors. Despite the name, these designs are largely based on unproven concepts from more than 50 years ago. Unlike conventional light-water reactors, these rely on sodium or molten salt or gas for cooling, and their proponents claim they will be less expensive, safer and more secure than their predecessors. Some claim that these innovative devices will be ready for prime time by the end of this decade.

This has naturally attracted the attention of Biden administration officials and some key members of Congress, who are looking for ways to curb carbon emissions. But an analysis of non-light-water reactor concepts in development by the Union of Concerned Scientists (UCS) has found that these designs are no better—and in some respects significantly worse—than the light-water reactors in operation today. The report's author, UCS physicist Edwin Lyman, took a close look at the claims developers have been making: that these new devices will burn uranium fuel more efficiently and produce less radioactive waste than existing plants; will reduce the risk of nuclear proliferation; and will be commercialized relatively soon. Those claims, however, do not hold up to scrutiny.

Elliott Negin is a senior writer at the Union of Concerned Scientists.

One contender, for example, TerraPower's 345-megawatt Natrium reactor, received considerable media attention earlier this year when company founder Bill Gates touted it during interviews about his new book, *How to Avoid a Climate Disaster*. According to the UCS report, however, sodium-cooled fast reactors such as Natrium would likely be less uranium-efficient and would not reduce the amount of waste that requires long-term isolation. They could also experience safety problems that are not an issue for light-water reactors. Sodium coolant, for instance, can burn when exposed to air or water, and the Natrium's design could experience uncontrollable power increases that result in rapid core melting.

In June, TerraPower announced that it would build the first Natrium reactor in Wyoming as part of a 50–50 cost-share program with the Department of Energy. The DOE program originally required the company to have the reactor, still in its early design stage, up and running by 2027. That was recently pushed back a year, but it is still a completely unrealistic timetable. According to the UCS report, if federal regulators require the necessary safety demonstrations, it could take at least 20 years—and billions of dollars in additional costs—to commercialize such reactors, their associated fuel-cycle facilities, and other related infrastructure.

The Nuclear Regulatory Commission (NRC) may have to adapt some regulations when licensing reactor technologies that differ significantly in design from the current fleet. Lyman says that should not mean weakening public health and safety standards, finding no justification for the claim that "advanced" reactors will be so much safer and more secure that the NRC can exempt them from fundamental safeguards. On the contrary, because there are so many open questions about these reactors, he says they may need to meet even more stringent requirements.

Lyman's report recommends that the DOE suspend its advanced reactor demonstration program until the NRC determines whether it will require full-scale prototype tests before any designs are licensed for commercial deployment, which the report argues are essential. It also calls on Congress to require the NRC to convene an independent commission to review the technical merits of non-light-water reactors and approve only those projects that have a high likelihood of commercialization and are clearly safer and more secure than the current fleet.

Finally, it recommends that the NRC and Congress consider spending more research and development dollars on improving the safety and security of light-water reactors rather than on commercializing immature, overhyped non-light-water reactor designs. Any federal appropriations for R&D and deployment of these reactor designs, Lyman says, should be guided by a realistic assessment of the likely benefits and not based on wishful thinking. SA

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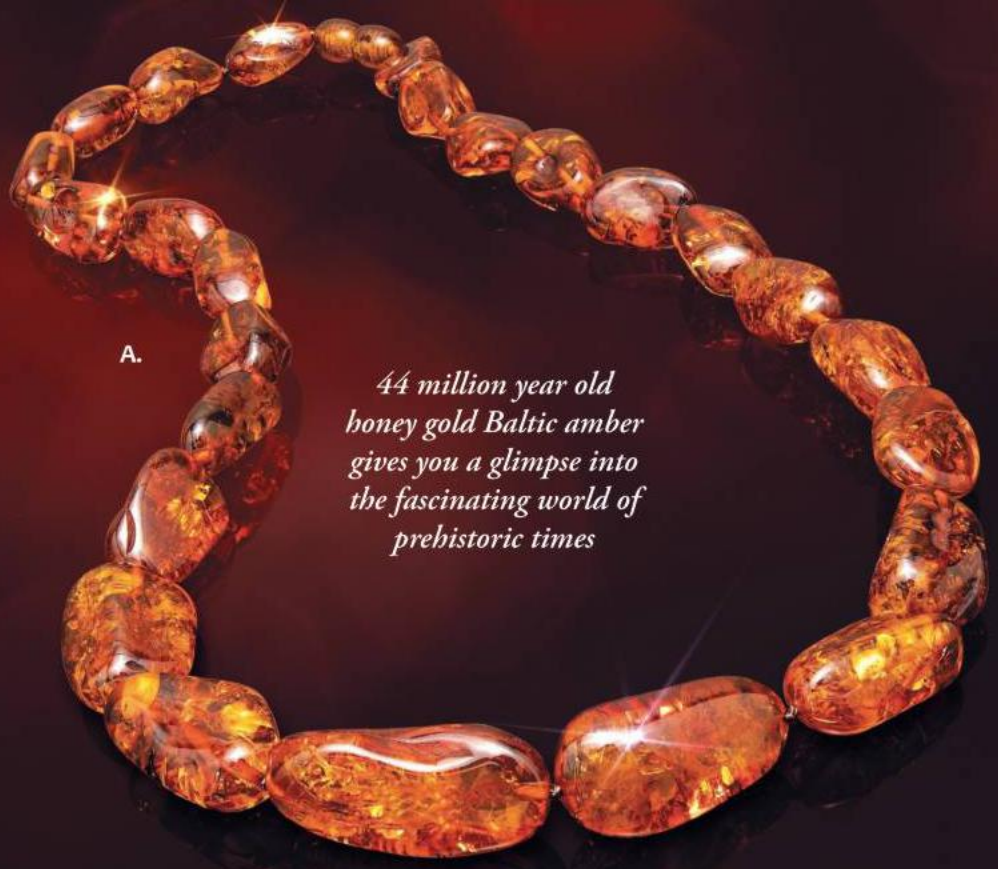
Illustration by Thomas Fuchs



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ADVANCES

Cyanobacteria growing in Yellowstone Lake, Wyo. Prehistoric species were the first to photosynthesize, helping to fill Earth's atmosphere with oxygen.

Jennifer Idol Stocktrek Images and Getty Images

INSIDE

EARTH HISTORY

An Oxygen Revolution

Changes in Earth's spin may have influenced the gas's buildup in the atmosphere

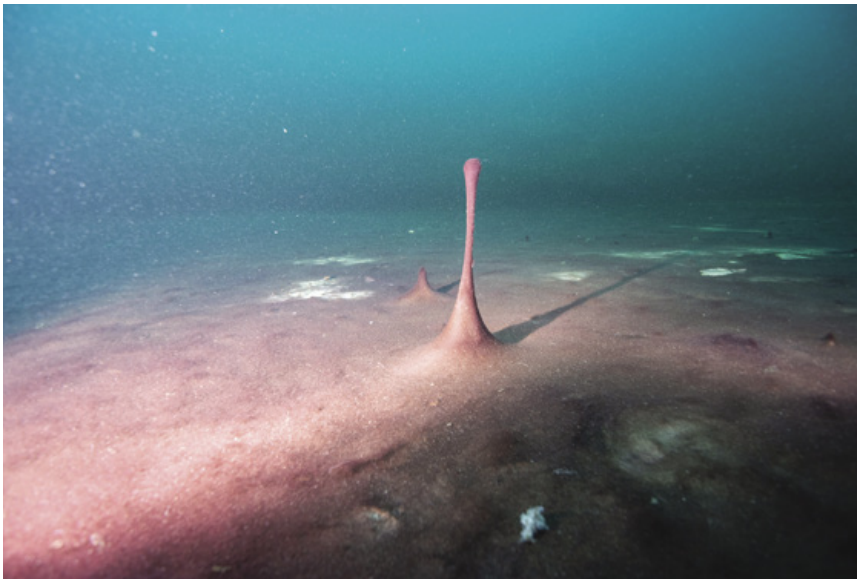
When Judith Klatt began studying the colorful mats of primitive microbes living in a sinkhole at the bottom of Lake Huron, she thought she might learn something about Earth's early ecosystems. Instead Klatt, a biogeochemist at the Max Planck Institute for Marine Microbiology in Bremen, Germany, wound up confronting one of geology's greatest unsolved mysteries: How, exactly, did Earth become the only planet known to have an oxygen-rich atmosphere?

Geologic clues suggest microbes may have started releasing oxygen via photosynthesis as early as three billion years ago or even before. But for some reason, it took about half a billion years for that oxygen to build up in the atmosphere and then a billion more for it to reach modern levels and set the stage for complex life. These delays have long puzzled scientists. Some have proposed that chemical reactions consumed much of the gas or that a lack of essential nutrients limited its production.

Now, inspired by the sinkhole work, Klatt and her colleagues have identified another possible explanation, which they describe in *Nature Geoscience*: early Earth's days were simply too short.

Soon after the solar system formed, a Mars-sized object crashed into Earth and sent up a spray of debris that became the

moon. Drag from our natural satellite has gradually slowed the planet's rotation ever since, increasing day length from about six hours in Earth's youth to 24 hours today. Scientists have known about this slowdown for decades and are continuing to refine the details. But few had linked it to oxygen levels—until University of Michigan oceanographer Brian Arbic heard a talk about Klatt's work with a Lake Huron sinkhole. Arbic, a co-author on the new paper, wondered whether changing day length could have affected photosynthesis over geologic time.



Gas bubbles out of a bacterial mat in the Lake Huron sinkhole, where cyanobacteria and sulfur-eating microbes vie for space.

Because it is fed by oxygen-poor, sulfur-rich groundwater, the sinkhole approximates conditions on early Earth, hosting communities of microscopic bacteria that blanket the lake bottom in purple and white mats. Klatt and her colleagues examined how photosynthesizing, oxygen-producing cyanobacteria lie hidden under sulfur-eating competitors at night—and how the two literally swap positions at dawn and dusk. The researchers found that the time they take to trade places creates a lag between when the sun rises and when photosynthesis ramps up, limiting how much oxygen the mats can generate on short days. In fact, Klatt showed in the laboratory that the mats produced no oxygen at all on artificial 12-hour "days" and that oxygen production increased with day lengths beyond 16 hours.

Klatt initially doubted that the sinkhole results could help explain the mystery of the oxygen. "It's a very special type of community that might not have existed in an ancient Earth," she says. And without such competition, changes in day length should not matter, because microbes would receive the same total amount of sunlight—just delivered in different increments. But eventually (after thinking for what she calls an "embarrassingly long" time), Klatt realized there was an even more basic link that would apply to any kind of bacterial mat, including those on early Earth: even if oxygen production remained unchanged, longer days would allow more gas to seep into the water—and ultimately into the atmosphere.

That is because the amount of oxygen leaving a mat is limited by how fast gas molecules can diffuse out of it and by how much is consumed by other kinds of bacteria in the mat. Longer days have a drawn-out peak in sunlight, letting more oxygen build up in the mat, which increases diffusion. Critically, longer days also give the gas more time to escape before nightfall, when oxygen-gobbling microbes consume the rest. These mechanisms could have had a strong impact on atmospheric oxygen levels over Earth's history, the study's modeling results suggest.

It's "a simple but elegant idea," says Timothy Lyons, a biogeochemist at the University of California, Riverside, who was not involved in the study. Lyons says there are still significant unknowns, such as whether early photosynthetic bacteria lived mostly on the seafloor or floated free in the water, where they could release oxygen more easily and without much dependence on diffusion. He suspects that many processes conspired to fill the atmosphere with oxygen—and that day length could certainly have contributed.

Other possible mechanisms include changing emissions of oxygen-consuming volcanic gases, such as hydrogen and methane, and limited supplies of phosphorus, a necessary nutrient for photosynthesis. Benjamin Mills, an Earth evolution modeler at the University of Leeds in England, who was not involved with the study, says he is surprised that scientists had mostly overlooked the role of day length. The challenge now, he says, is assessing "the relative importance of this process versus the other things we know about the global oxygen cycle."

Both Mills and Purdue University astrobiologist Stephanie Olson, who was also not involved in the study, were impressed by how well the new results match the history of atmospheric oxygenation, including the famous two-step rise and the intervening "boring billion" years—when oxygen levels flat-lined, and day length also stalled at 21 hours. "It's intriguing that the pattern of oxygen accumulation and the tempo of the slowing of Earth's rotation rate seem to have occurred in lockstep," Olson says.

Olson is one of the few others to have proposed a connection between day length and oxygen levels. In a 2020 paper that primarily focused on exoplanets, she described how changes in Earth's rotation over time might have affected ocean circulation and thus the transport of nutrients such as phosphorus that fuel photosynthesis. Olson and her students are now exploring the idea with computer models. This mechanism and Klatt's could have worked in concert, Olson says: "I see them as highly complementary, not competing, ideas."

The thought of a connection between Earth's rotation and atmospheric oxygen still amazes Arjun Chennu, an ecologist at the Leibniz Center for Tropical Marine Research in Bremen, who co-led the study with Klatt. From the motion of planets to the movement of molecules, he says, "the range of scales at which these interactions have an effect … is wild." —*Julia Rosen*

Phil Hartmeyer and NOAA Thunder Bay National Marine Sanctuary

IN THE NEWS

Quick Hits

By Tess Joosse

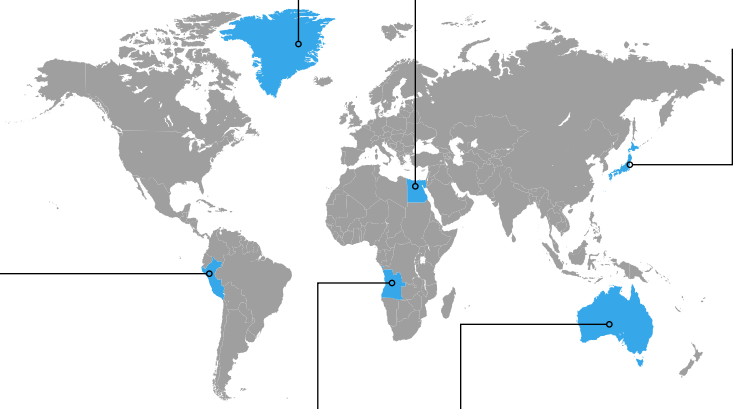
For more details, visit www.ScientificAmerican.com/nov2021/advances

GREENLAND

Scientists compiled evidence suggesting polar bears can use rocks or ice chunks to bludgeon walruses to death, supporting centuries-old Inuit reports. Although the practice likely is infrequent, it would help to more easily take down the huge, thick-skulled animals.

EGYPT

Archaeologists unearthed a 43-million-year-old fossil of a now extinct four-legged whale from part of the Sahara Desert that was once a vibrant sea. The 10-foot-long animal had a jaw like a crocodile's and lived both in water and on land.



PERU

A 6,000-year-old human skeleton found in the ancient coastal village of Paloma might be part of the oldest-known shark-attack victim. The skeleton's left leg is missing, and its right arm bears deep, distinctive bite marks.

JAPAN

Researchers successfully bred mice from freeze-dried sperm shipped 200 kilometers from Kyoto to Kofu on a postcard via standard mail delivery. Their new preservation process will let scientists at different institutions efficiently share specialized mouse genotypes without freezing agents or breakable glass vials.

ANGOLA

A desert plant called Welwitschia sports only two leaves—but can grow them continuously for millennia, with some specimens more than 3,000 years old. New research shows the species has many copies of metabolism- and cell-growth-related genes, helping it persist through periods of environmental stress.

AUSTRALIA

A detailed new soil map of Canberra will help police pinpoint where a sample of dirt originated. The data set has more than 100 variables, including pH, color and chemical makeup, which can link soil found on evidence or suspects to a specific location.

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[1] Source: Global Cement and Concrete Association
[2] Annual global cement production in 2019: 4.1 billion tons. Precast industry is 30% of total. Source: IEA.
[3] Typical passenger vehicle emits around 4.6 metric tons of CO_2 per year. Source: EPA.


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[1] IEA (2017), The Future of Trucks, IEA, Paris
[2] IEA (2020) CO_2 emissions from heavy-duty vehicles in the Sustainable Development Scenario, 2000–2030
[3] One young tree absorbs 5.9kg CO_2 per year. Source: Urban Forestry Network.

EVOLUTION

Venomous Secret

How fangs evolved over and over

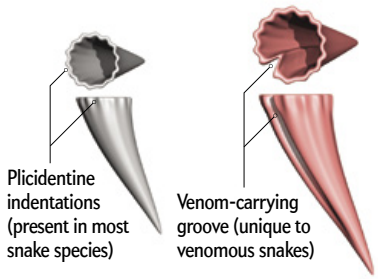
Gaboon viper skull shows prominent fangs.

Joe McDonald *Getty Images (skull)*; From "Plicidentine and the Repeated Origins of Snake Venom Fangs," by **Alessandro Palci,** in *Proceedings of the Royal Society B*, Vol. 288; August 11, 2021 (*tooth scans*)

The world hosts hundreds of wildly different venomous snake species, from brightly banded coral snakes to camouflaged cottonmouths. But somehow even distantly related species independently evolved specialized fangs with venom-carrying grooves—a longtime puzzle spurring new research into how this could have happened. The answer, says Flinders University herpetologist Alessandro Palci, has been hiding inside the serpents' mouths all along.

It turns out that the teeth of most snake species, Palci and his co-authors report in the *Proceedings of the Royal Society B*, have a ring of tiny indentations around their bases. This pitted tooth tissue, called plicidentine, helps to anchor the teeth to the jaws. "Before our study, plicidentine was thought to be limited to only three types of lizards among living reptiles," Palci says. In fact, the study finds, it seems to be ubiquitous in snakes.

And these dental anchors have taken on another function in venomous species, the researchers say. They used microscopic tissue sampling and micro CT scans of snake teeth to determine that in the teeth



nearest a snake's venom glands, the plicidentine's folds have evolved into longer grooves that help snake venom flow from gland to tooth—and then into prey.

This result suggests that modern venomous snake species did not have to start from evolutionary scratch every time they developed a deadly bite. Many snakes produce toxic saliva, Palci notes, and a tooth with a more pronounced plicidentine groove lets that incipient venom travel more efficiently. Repeat this change in generations of snakes, and venom-delivering fangs will evolve.

"I love seeing modern imaging technology and beautiful micro CT scans applied to a classic question," says Whitman College herpetologist Kate Jackson, who was not involved in the new study. Snakes may have developed venom-delivering teeth via other routes as well, Jackson adds. For instance, many fish-eating species have grooved teeth that help to grip slippery prey; these grooves could also have evolved into venom channels. Nevertheless, she says, the study reveals a new common feature of snakes and can inform herpetologists' understanding of how snake fangs evolved anew time and again. —*Riley Black*

FLUID DYNAMICS

Bubble Power

Vibrations could decrease energy needed to process minerals

Pulling essential minerals from the ground is dirty work, and most of the stuff miners extract is useless sediment. In some Chilean copper mines, for instance, hundreds of thousands of tons of material are processed every day, "but 95 percent of that is waste," says D. R. Nagaraj, a mining industry expert at Columbia University. To sift out precious minerals, engineers often blow air bubbles through the material in a setup called a bubbling fluidized bed—and a new twist could make this costly process more efficient.

In the current system, sediment is pushed up through a chamber by air bubbles, separating particles of different sizes so dirt can be skimmed off the top. But the procedure uses a lot of water and energy, partially because the air bubbles' chaotic motion reduces their efficiency, says Columbia University chemical engineer Chris Boyce. "They're coalescing and splitting and not maintaining a uniform size," he explains, making the sorting process uneven.

In the *Proceedings of the National Academy of Sciences USA*, Boyce and his colleagues describe a way of keeping the bubbles in line, requiring less energy to separate minerals from refuse. They mounted the bubble-filled chamber on a platform vibrating at a consistent clip and found that otherwise chaotic air pockets lined up into ascending rows as the system shook. The vibrations make dirt particles shift between solid and fluidlike states, sometimes behaving like sand in a sandcastle, sometimes acting like grains in an hourglass, Boyce says. The researchers documented how this rapid shifting pushes the bubbles into formation—a process that previous models of gas-solid interactions could not predict, the team writes.

The experimental results held for varying apparatus and particle sizes. This bodes well for the shift in magnitude from laboratory to industry, Boyce says.

That's "the key question," says McGill University materials engineer Kristian Waters, who was not involved in the study. "How can we scale up this process? Some mines are working at hundreds of thousands of tons a day in ore."

Boyce is now collaborating with experts such as Nagaraj to put the findings to work reducing mining's environmental footprint. Even green technologies such as electric cars need minerals, Nagaraj says, so "if mining is not sustainable, nothing else will be." —*Tess Joosse*

Jack Andersen *Getty Images*

CHEMISTRY

Beer's Complexity

Chemical insight reveals thousands of compounds that make up a brew

Given its 13,000-year history, one might assume we'd have beer figured out by now. But recent research examines the bubbly liquid's composition with unprecedented focus, singling out a new quality-control measure.

Beer contains three complex organic ingredients: grain, hops and yeast. Throughout the brewing process, these all interact with one another's by-products, creating hundreds of chemical derivatives that can influence taste. Although some food chemists consider beer's complexity daunting, Stefan Pieczonka, a Technical University of Munich researcher pursuing what he calls a "Ph.D. in beer," saw untapped potential in it. Working with T.U.M. chemist Philippe Schmitt-Kopplin, Pieczonka ran 400 samples of commercially available beers through a high-powered mass spectrometer—a machine that teases apart mixtures of chemicals and identifies them by splitting their molecules into charged ions, which it sorts using magnetic fields. The team also ran a subset of the beers through a second type of mass spectrometer, and Schmitt-Kopplin says combining these processes let the researchers identify more than 7,000 unique ions never before found in beer. Working backward, they deduced the tens of thousands of molecules giving rise to these ions and traced each molecule to one of the original ingredients of the brew. (Leftover samples made for exciting lab happy hours, the researchers add.)

One newfound molecule originated from a reaction among compounds in yeast, hops and rice—the last sometimes contaminates brewery tools or batches of grains for brewing. As no quality-control test currently exists for detecting rice in beer as a contaminant or allergen, the researchers propose testing for this new chemical. Their new work is detailed in *Frontiers in Chemistry*.

Beer expert Gwen Conley, who directs quality and innovation at Cutwater Spirits and was not involved in the research, says such a test could augment quality assurance for both beer and distilled spirits. "When it comes to beer," she says, "every single stage could be tested."

Knowing more about a beer's ingredients can also aid historical research efforts. Pieczonka and Schmitt-Kopplin are running the same analysis on an 1885 German beer to learn more about 19th-century brewing practices—and to re-create its taste.

—Maddie Bender

ECOLOGY

Seabird Hotspot

Millions of birds converge on a stretch of the North Atlantic

Halfway between Scotland and Bermuda, a wild expanse of ocean draws millions of seabirds from vast distances every year. A new study published in *Conservation Letters* uses decades of tracking data to document that at least five million migratory birds, representing about two dozen species from both hemispheres, rely on a North Atlantic hotspot of almost 600,000 square kilometers for food.

Ecologists have long suspected that the North Atlantic served as a critical foraging zone for migrating seabird species, but they lacked data on birds' travel patterns to justify protecting these international waters.

Migratory seabirds are "one of the most threatened taxa today," says Tammy Davies, a conservation scientist at BirdLife International and lead author of the study. Seventeen of the 21 species studied, including Atlantic puffins, Arctic terns and Bermuda petrels, face declining populations. The birds are harmed by pollution, overfishing and industrial fishing operations that net the animals along with their catches. Although seabirds' breeding zones on land tend to be protected, their foraging sites are typically in the high seas, beyond any country's jurisdiction.

Analyzing individual birds' satellite-tracked migration patterns, the researchers were stunned by their sheer numbers and diversity, as well as how steadily this part of the ocean is used year-round. "What's surprising is the amount of species congregating in this area and the distances that some seabirds are traveling to the site," Davies says. "You have birds in the remote South Atlantic traveling 13,000 kilometers to forage in this site. Clearly, something fantastic is there which is making these birds take these journeys."

The "something fantastic" is likely a buffet delivered by converging ocean currents, suggests a complementary study in *Progress in Oceanography*. It paired satellite data and computer modeling with old-fashioned birdwatching from a ship that crossed the North Atlantic in 2017. "I think there's still a lot to be learned by going and actually looking," says University of

ENVIRONMENT

Mercury Flow

Large amounts of the toxic metal follow rivers to coastal food supplies

Rivers may carry as much as 1,000 tons of mercury to the world's coastlines every year, researchers report in *Nature Geoscience*. This would make rivers the main way this potent neurotoxin reaches coastal oceans, where it most threatens public health.

Human mercury exposure is largely linked to coastal fisheries, where the heavy metal accumulates in marine life that we eat. But relatively little of this pollution originates along coastlines; much comes from inland sources such as wildfires, mines and coal-burning power plants. Scientists have long thought this mercury traveled primarily through the atmosphere as vapor or bound to small particles. But the new findings suggest rivers are the greatest pathway for coastal mercury.

Yale University biogeochemists Maodian Liu and Peter Raymond worked with colleagues to combine mercury measurements from rivers around the world with

Rivers curl through an island in West Africa's Guinea-Bissau.

SI Imaging Services *Imazins* and *Getty Images*

data and simulations describing how sediment and biological forms of carbon move through waterways. "These two elements [mercury and carbon] are linked because mercury is often bound to organic carbon in soils and rivers," Raymond says. The researchers' new model indicates that rivers could carry approximately three times more mercury to the coasts than the atmosphere does—and that half of this total can be traced to the planet's 10 largest rivers.

Researchers have estimated the amount of mercury transported by rivers before. But most such studies "are really very basic," says Mediterranean Institute of Oceanography researcher Lars-Eric Heimbürger-Boavida, who was not involved in the new study. Most previous work used average concentrations extrapolated from measurements made in certain rivers, he notes, with researchers "assuming that other rivers work the same way." Heimbürger-Boavida praises the study's use of a large, worldwide data set but cautions that other research might define "coastal" differently, leading to a different final esti-

Illustrations by Thomas Fuchs

Glasgow ecologist Ewan Wakefield, lead author of the *Oceanography* study.

Within the hotspot, seabirds stuck to these food-rich currents, Wakefield says. The researchers even noticed different species hanging out in different currents, most likely driven by dietary preferences and variations in foraging behaviors such as diving.

"It's really incredible to see one place that is so singularly important … for some of the smallest seabirds on up to some of the really big wanderers," says Smithsonian ecologist Autumn-Lynn Harrison, who was not involved in either study. "It's a really unifying place."

The researchers hope these new data will lead the international Convention for the Protection of the Marine Environment of the North-East Atlantic to designate the seabird hotspot a Marine Protected Area—and maybe set a precedent for shielding other areas in the high seas. —*Rebecca Dzombak*

mate of rivers' impact as compared with the atmosphere's.

According to Susan Egan Keane, a public health specialist at the Natural Resources Defense Council, models of the mercury cycle—how the substance enters, leaves and moves through the environment—are "the bread and butter" of mercury risk assessments. "That's how one predicts how changes in emissions … translate into predicted changes in fish concentration, which translate into changes in exposure to human beings," she says.

The researchers note that many large rivers are expected to flush more water and sediment to the coasts as the climate warms, and this process could increase mercury transport. Thawing permafrost and shifting ocean temperatures could also affect the mercury cycle, Keane says.

Understanding rivers' role is a step toward a more complete understanding of this cycle—knowledge that could help experts anticipate and respond to mercury hazards in an uncertain future and better predict how our planet will react to global efforts to reduce mercury emissions. —*Elise Cutts*

Source: "Imperfect Comb Construction Reveals the Architectural Abilities of Honeybees," by **Michael L. Smith, Nils Napp and Kirstin H. Peterson,** in *Proceedings of the National Academy of Sciences USA*, Vol. 118; August 3, 2021

ANIMAL BEHAVIOR

Active Architects

Honeybees nimbly adapt comb-building construction tactics

Charles Darwin described bees' ability to build perfect honeycombs as "the most wonderful of all known instincts." Each hexagonal cell is so precisely constructed and so neatly arrayed that a comb is a visual treat. Now new research into how honeybees incorporate different cell sizes into a flawless-looking grid—and seamlessly merge combs built from multiple directions at once—reveals remarkable adaptability.

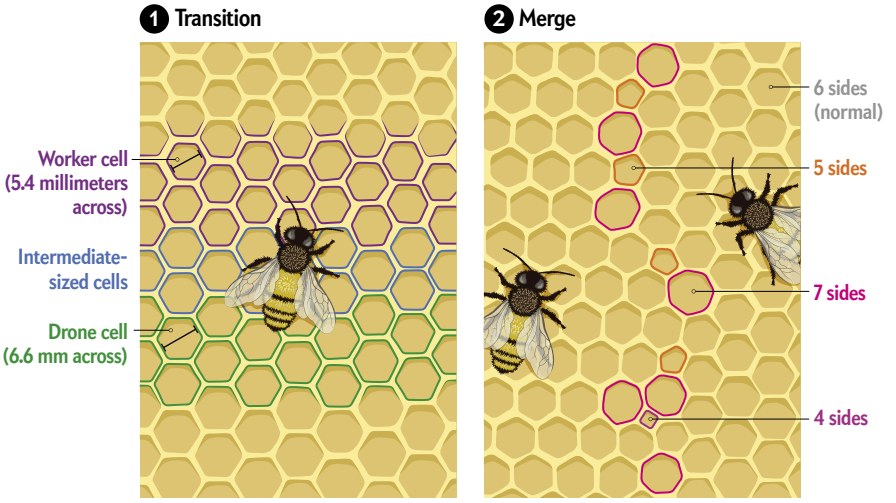
Adjacent honey storage cells are typically uniform in size, but bees must build some larger cells for rearing drones and smaller ones for workers. They also have to align and join comb grids being constructed from separate starting points. Understanding how bees accomplish all of this so elegantly "is an old quest," says Auburn University behavioral ecologist Michael Smith.

For a study in the *Proceedings of the National Academy of Sciences USA*, Smith and his colleagues measured 19,000 comb cells from 12 colonies of Italian honeybees. Using automated image analysis, they examined the centers and vertices of these cells to find variations in their shapes and sizes. "We just couldn't extract the precise measurement of thousands of cells until we had this new automated method," Smith says.

The researchers found that bees made clever adjustments to transition between sizes and merge combs as cleanly as possible. The insects utilized patterns of irregular shapes (mostly pairs of heptagons and pentagons) and manipulated comb cells' size and orientation so craftily that their ability can be considered "a true architectural skill," the researchers write.

"The hexagonal grid structure of a honeycomb—constructed by a leaderless collective of hundreds of bees—lends itself to speculation that robotic, innate behavior must be at work," says Queen Mary University entomologist Lars Chittka, who was not involved with the study. "But a simple robot does not have such a level of adaptability and rate of error recovery."

Raghavendra Gadagkar, who studies insect behavior at the Indian Institute of Science, Bangalore, and who was also not part of the study, suggests that examining how bees coordinate comb building can help advance robotics. "Imagine," he says, "if we could program such wits of honeybees in real-world robots." —*Saugat Bolakhe*



Bees are known for building honeycombs composed of perfectly uniform hexagons, but they deviate from their regular patterns when necessary. For example, when transitioning between small cells for rearing worker bees and those meant for larger reproductive drones, the bees build one or two rows of intermediate-sized cells 1. And because they start construction in multiple locations, bees must find ways to merge sections to form a single comb, an operation that often involves combinations of 4-, 5- and 7-sided cells 2.

Illustration by Brown Bird Design

METEOROLOGY

Science in Images

By Leslie Nemo

When conditions align perfectly, disaster comes rushing across the Great Plains: a supercell storm, recognizable by a wide, anvil-shaped formation at its top, can unleash hail, lightning and tornadoes. Seen here is a supercell near West Point, Neb.

These relatively rare storms can last hours. A supercell thrives on upward-moving warm air and downward-moving cold air; because the two streams travel separate paths, the latter does not hinder the former, which prolongs the life of the storm. Although just 20 percent of supercells generate tornadoes, they account for most of the twisters that tear up parts of the U.S. every year.

In short, a supercell on the horizon is an ominous sign. But meteorologists are not sure what makes these storms turn deadly or how often they do so. This is why researchers have spent decades flying into and driving by supercells, evaluating what it takes for one to create hazardous conditions—especially tornadoes. If scientists can develop a better sense of when a tornado will touch down, officials can warn the public earlier and increase local residents' trust in forecasts.

To get a better idea of when the storms create tornadoes, researchers have also begun flying drones into supercells rumbling across Nebraska, South Dakota, Kansas and several other states. Plus, detailed computer simulations of supercells may help identify what conditions lead to tornadoes, although this kind of study is a slow process: an in-depth simulation on one of the world's most

Mike Hollingshead *Alamy Stock Photo*

powerful supercomputers took three months to finish.

Historically, tornadoes are most common in the Great Plains, but evidence is building that such extreme weather events are becoming more frequent farther east, such as in Mississippi, Alabama and Tennessee. Someone has to witness a tornado for it to be officially recorded, and because population density has increased since the early 1900s, scientists are still untangling whether twisters are indeed more common and if supercells are to blame—or if more people are simply around to see them.

For more, visit www.ScientificAmerican.com/science-in-images

PHYSICS

Flat Attraction

Magnets one atom thick unlock better info storage

From computers to credit cards to cloud servers, today's technology relies on magnets to hold encoded data in place on a storage device. But a magnet's size limits storage capacity; even a paper-thin magnet takes up space that could be better used for encoding information.

Now, for a study published in *Nature Communications*, researchers have engineered a magnet among the world's thinnest—a flexible sheet of zinc oxide and cobalt just one atom thick. "That means we can store larger amounts of data using the same amount of materials," says University of California, Berkeley, engineer Jie Yao, the study's senior author.

Beyond slimming down conventional data storage, magnets less than one nanometer thick are indispensable for developing spintronics (short for spin electronics): gadgets that use an electron's spin direction, rather than its charge, to encode data. Such magnets could even help excite electrons into a "quantum superposition," which lets particles occupy multiple states simultaneously. That way, data could potentially be stored using three states—spinning up or down, or both ways at once—instead of the usual two.

Ordinarily, nanoscale magnets must be supercooled to temperatures as low as −320 degrees Fahrenheit to maintain magnetic fields. This requirement presents a big obstacle to creating commercial spintronic devices or shrinking conventional data storage. "You don't want to carry a cryogenic cooler with you," says University of Chicago spintronics researcher David Awschalom, who was not involved in the study. "So having a material that's compact and flexible at room temperature is quite important."

The new magnet's two-dimensional lattice functions perfectly at room temperature—and it even stays magnetized in conditions hot enough to boil water. The decision to combine these particular elements was critical; zinc and oxygen by themselves are not magnetic, but they interact with magnetic metals such as cobalt. By adjusting the ratio of cobalt atoms to zinc oxide molecules, the team "tuned" the materials' magnetic intensity. Around 12 percent cobalt was their sweet spot—at less than 6 percent the magnet was too weak to be effective, and at more than 15 percent it became unstable.

Yao thinks wandering electrons from the zinc oxide help to stabilize the cobalt atoms, keeping the magnetic field intact. "The current hypothesis," Yao says, "is that the electrons serve as a messenger that allows these cobalt atoms to 'talk' to each other."

Computational physicist Stefano Sanvito of Trinity College in Ireland, who was also not involved in the study, says the magnet's usefulness will depend on how it interacts with other 2-D materials. Stacking layers of various single-atom films "like a deck of cards," he says, will let engineers tailor the next generation of spintronics for a host of applications, from secure data encryption to quantum computing: "It's going to be very fun." —*Joanna Thompson*

PLANETARY SCIENCE

Martian Puddles

The Curiosity rover's landing site may not be what it seems

Of all the discoveries made by NASA's Curiosity Mars rover, the most epochal has been that its landing site, Gale Crater, once held a massive and long-lasting lake. Now, however, a new study suggests this "lake" may have only been a series of smaller, transient puddles.

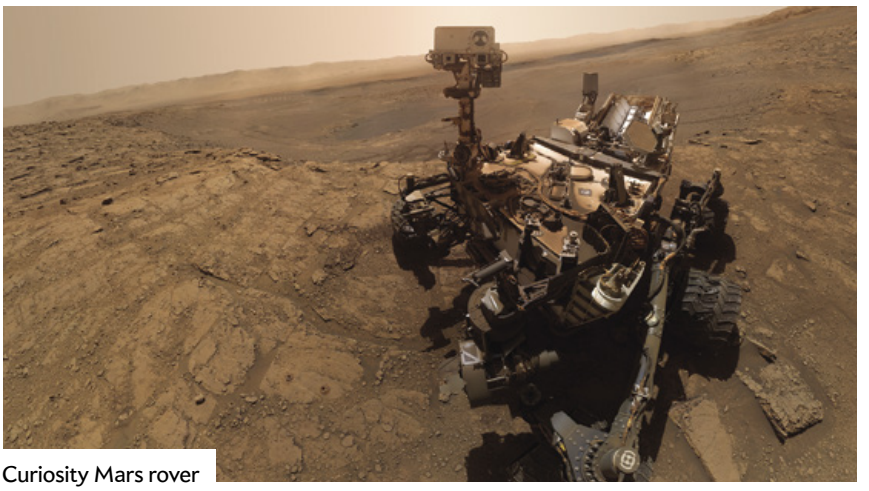
Curiosity landed and began exploring Gale Crater in 2012. Mere months later, at the base of 5.5-kilometer Mount Sharp in the crater's center, the rover found layers of mudstone—suggestive of sediments that had settled in standing water—as well as flow-rippled rocks from an ancient stream. As Curiosity ascended Mount Sharp's base, it also detected water-altered minerals strewn across the mountain. The conclusion seemed almost inescapable: About 3.7 billion years ago Gale had harbored a large reservoir for perhaps millions of years, during which it could have been a microbial haven. And Mount Sharp slowly formed below the waves from sediments swept into the lake.

A new interpretation, published in *Science Advances* by University of Hong Kong planetary scientists Jiacheng Liu, Joe Michalski and Mei-Fu Zhou, posits instead that Mount Sharp arose in the open air from windblown sediments and was then weathered by water: short-lived ponds formed by rainfall sent liquid trickling through the sediment. Microbes could have still thrived in those scant surface waters but only for a relatively brief time—within a few tens of thousands of years, any ponds on Mount Sharp and at its base would have vanished. These conclusions come from chemical patterns in a group of sedimentary rocks, called the Murray formation, that Curiosity sampled along its path up Mount Sharp.

"Jiacheng took a very close look at the elemental abundances and mineral occurrences, as measured by the rover, from the base of the crater up through more than 400 meters of [exposed rock layers] visited during the first eight years of the mission," Michalski says. The analysis revealed a gradual change as the rover climbed: Elements such as iron, which are more easily washed away by water, became scarcer at higher altitudes; less soluble elements such as aluminum became more prevalent. This pattern is broadly consistent with rainfall-driven "top-down" weathering seen in many rock formations on Earth.

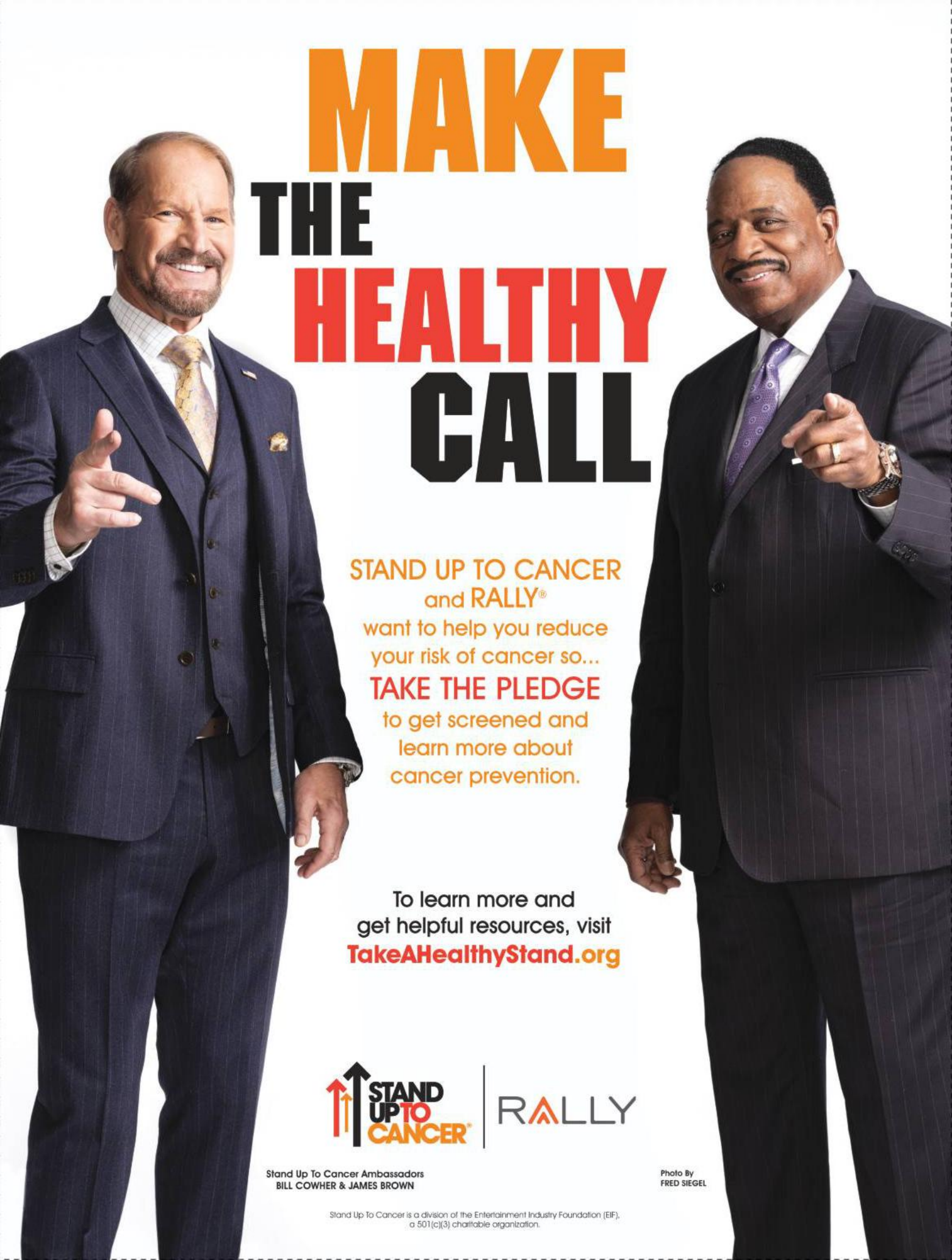
"If true, this result would call into question our understanding of the origin of sedimentary-rock mountains on Mars," says Edwin Kite, a planetary scientist at the University of Chicago, who was unaffiliated with the study. But, he adds, confirming the "ground truth" at Gale Crater requires tools Curiosity lacks, such as a very high-resolution x-ray spectrometer to better assess shifting elemental abundances. Curiosity's sister rover, Perseverance, carries just such an instrument—but is located thousands of kilometers away, in Jezero Crater.

For now, in the absence of more conclusive data, the Curiosity team is sticking by its original interpretation, says Kirsten Siebach, a Rice University planetary scientist and member of the Curiosity and Perseverance science teams. "I'm not convinced it's time to change our story of Gale Crater," she says, "but as we gather new evidence we always have to be open to refining our past conclusions." —*Lee Billings*



Curiosity Mars rover

NASA, JPL-Caltech and MSSS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The Way of Karma

Composition by Monica Ong ("The Way of Karma" Collage with archival Auntie Betty and map of the Milky Way): "The Starry Grandeur of the Milky Way" from *The Circle of Knowledge: A Classified, Simplified, Visualized Book of Answers*. Editor in chief: Henry W. Ruoff, M.A., Lit.D., D.C.L.; The Standard Publication Company, Boston, 1916, page 22 (*Milky Way*)

Monica Ong is a visual poet whose debut collection, *Silent Anatomies*, won the Kore Press First Book Award in poetry in 2015. Ong is a Kundiman poetry fellow and graduate of Rhode Island School of Design. Her work has been exhibited nationally and resides within many distinct institutional collections. Ong is also founder of Proxima Vera, a micropress specializing in literary art and objects.

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Claudia Wallis is an award-winning science journalist whose work has appeared in the *New York Times, Time, Fortune* and the *New Republic*. She was science editor at *Time* and managing editor of *Scientific American Mind*.

Painkiller Risks

Advil, Tylenol and the like—increasingly used to replace opioids—have downsides

By Claudia Wallis

After tens of thousands of overdose deaths and billions of dollars in lawsuits, the medical establishment has gotten the memo on opioids. Instead of prescribing OxyContin or Percocet for acute pain, doctors are increasingly offering patients prescription-level doses of popular painkillers sold over the counter: acetaminophen (Tylenol) and nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin or Advil). Five hundred milligrams (mg) of acetaminophen given with 200 mg of ibuprofen is more effective than opioids for postoperative pain and dental pain, research has shown, and the combo causes fewer side effects, with essentially no risk of addiction. NSAIDs are good even for excruciating kidney stones and minor fractures. And they are safer than and at least as effective as opioids for arthritis pain and lower backaches.

Still, there is no such thing as a risk-free drug, and that goes for our most trusted painkillers. Beyond dangers that have been known for decades—NSAIDs can irritate the gastrointestinal tract and cause serious bleeding; acetaminophen in daily doses of more than 4,000 mg can poison the liver—additional problems have emerged in more recent years. As our reliance on these pills grows, it makes sense to take a closer look at their potential harms and why they occur. "With this mad rush to get people off opioids, we will undoubtedly start to see an increase in adverse events from NSAIDs and acetaminophen. It's inevitable," says Sean Mackey, chief of pain medicine at Stanford University.

In addition to causing bleeding, almost all NSAIDs—aspirin is the exception—can raise the risk of heart attacks, strokes and heart failure. These dangers came into sharper focus in the early 2000s after the release of a new kind of NSAID called COX-2 inhibitors, which block an enzyme called cyclooxygenase-2 (most NSAIDs target both COX-1 and COX-2 enzymes). Designed to be easier on the gut, they proved rough on the circulatory system, and two of these drugs were withdrawn. (A third, celecoxib, or Celebrex, remains on the market.) These events prompted more scrutiny of other non-aspirin NSAIDs, and all were found to carry cardiovascular risks. In 2015 the U.S. Food and Drug Administration strengthened warnings about the dangers, which are greatest for people with heart disease or risk factors for it. That does not mean Advil and Aleve (naproxen) are off-limits for heart patients when they twist an ankle or strain their back, says Christian Ruff, director of cardiology at Brigham and Women's Hospital in Boston. "What I tell patients is to use NSAIDs for short periods and to take the lowest dose that provides the necessary pain relief."

Because they inhibit COX enzymes, which play a downstream role in everything from blood clotting to tissue repair, NSAIDs affect the cardiovascular system in multiple ways. "They increase heart attack and stroke risk by promoting clotting," Ruff explains. "They can impair wound healing after a heart attack, and they promote fluid and salt retention, which can overburden the heart and cause it to fail." NSAIDs can also damage the kidneys, which in turn burdens the heart. Aspirin does not cause these issues, but because it raises the odds of bleeding, it is no longer widely used for pain relief, nor is it as widely recommended for preventing heart attacks.

The impact on kidneys underlies dangers during pregnancy. Last year the FDA warned against taking NSAIDs at 20 weeks or later in pregnancy, when they might harm fetal kidneys and thereby cause low levels of amniotic fluid. People who cannot take NSAIDs because of heart or kidney disease or pregnancy are often advised to use acetaminophen, also called paracetamol. Though useful for pain and fever, this drug, unlike NSAIDs, does not reduce inflammation, and it has an unusual safety profile. "It is very safe up to a certain threshold, and above that line it is very hazardous," says Erin Krebs, a pain researcher and professor of medicine at the University of Minnesota. Krebs says it's "crazy" that the drug is present in more than 600 products (such as cold and flu formulas) because that makes it all too easy to go overboard. In the U.S., acetaminophen poisoning has displaced hepatitis as the most common reason people need a liver transplant.

Still, with judicious use, most people can take these painkillers without incident. "It's more challenging if you are going to use them long term," Mackey says. "When people stay on NSAIDs chronically, we monitor them with blood work and make sure they take the stuff with food and fluids." Individuals vary greatly in their response to analgesics, whether an NSAID, Tylenol or any of the scores of prescription drugs used for pain. Mackey often has patients try several before landing on what works best. "But understand," he notes, "that everything we put inside us carries some risk. There's no free lunch."

Illustration by Fatinha Ramos

CLIMATE

Vapor Storms

More moisture in a warmer atmosphere is fueling intense hurricanes and flooding rains

By Jennifer A. Francis

Illustration by Mark Ross

Jennifer A. Francis is a senior scientist and acting deputy director of the Woodwell Climate Research Center. She has done extensive research on Arctic warming and on atmospheric vapor and energy. She is a member of *Scientific American*'s board of advisers.

THE SUMMER OF 2021 WAS A GLARING EXAMPLE OF WHAT DISRUPTIVE WEATHER will look like in a warming world. In mid-July, storms in western Germany and Belgium dropped up to eight inches of rain in two days. Floodwaters ripped buildings apart and propelled them through village streets. A week later a year's worth of rain—more than two feet—fell in China's Henan province in just three days. Hundreds of thousands of people fled rivers that had burst their banks. In the capital city of Zhengzhou, commuters posted videos showing passengers trapped inside flooding subway cars, straining their heads toward the ceiling to reach the last pocket of air above the quickly rising water. In mid-August a sharp kink in the jet stream brought torrential storms to Tennessee that dropped an incredible 17 inches of rain in just 24 hours; catastrophic flooding killed at least 20 people. None of these storm systems were hurricanes or tropical depressions.

Soon enough, though, Hurricane Ida swirled into the Gulf of Mexico, the ninth named tropical storm in the year's busy North Atlantic season. On August 28 it was a Category 1 storm with sustained winds of 85 miles per hour. Less than 24 hours later Ida exploded to Category 4, whipped up at nearly twice the rate that the National Hurricane Center uses to define a rapidly intensifying storm. It hit the Louisiana coast with winds of 150 miles an hour, leaving more than a million people without power and more than 600,000 without water for days. Ida's wrath continued into the Northeast, where it delivered a record-breaking 3.15 inches of rain in one hour in New York City. The storm killed at least 80 people and devastated a swath of communities in the eastern U.S.

What all these destructive events have in common is water vapor—lots of it. Water vapor—the gaseous form of H_2O—is playing an outsized role in fueling destructive storms and accelerating climate change. As the oceans and atmosphere warm, additional water evaporates into the air. Warmer air, in turn, can hold more of that vapor before it condenses into cloud droplets that can create flooding rains. The amount of vapor in the atmosphere has increased about 4 percent globally just since the mid-1990s. That may not sound like much, but it is a big deal to the climate system. A juicier atmosphere provides extra energy and moisture for storms of all kinds, including summertime thunderstorms, nor'easters along the U.S. Eastern Seaboard, hurricanes and even snowstorms. Additional vapor helps tropical storms like Ida intensify faster, too, leaving precious little time for safety officials to warn people in the crosshairs.

Scientists have long anticipated that climate change would create more airborne vapor, fueling

what might be called "vapor storms" that are unleashing more rain and snow than storms did only a few decades ago. Measurements confirm that heavy-precipitation events are hitting harder and occurring more often across the U.S. and the globe. Since the late 1980s about one third of U.S. property damage caused by flooding—$73 billion—has been attributed to increases in heavy precipitation.

In August 2017, for example, Hurricane Harvey dumped a mind-boggling five feet of rain in some Houston neighborhoods over the five days it dawdled in the region, leaving even well-weathered meteorologists speechless. At times the rainbands dropped an astounding six inches of precipitation per hour. One analysis concluded that the record-smashing rainfall was made three times more likely and 15 percent more intense by climate change, in particular the moisture-laden air that fed Harvey from the abnormally warm Gulf of Mexico.

Unlike most other atmospheric gases, water vapor is not evenly distributed around the globe. Vapor is abundant in the steamy tropical regions straddling the equator. From there, long tendrils of moisture can extend toward the cooler, drier poles along storm tracks, bathing mid- and high-latitude regions in bouts of intense, prolonged precipitation. These rivers of heat and moisture help to balance Earth's atmospheric energy distribution—and they are creating strong vapor storms along their path.

ENERGY PUMP

WHEN WE SWEAT under a hot sun or set a pot to boil on our kitchen stove, we convert liquid water into water vapor. The necessary ingredient is heat. Similarly, heat in the climate system causes water in moist soil, plants, oceans, lakes and streams to evaporate into the air. The vapor carries with it a form of energy called latent heat. If the vapor later condenses back into liquid—forming a cloud or dew on a lawn—that heat is released into the atmosphere. The resulting bubble of warm air is lighter than the air around it, so it rises. Because temperatures are generally cooler at higher altitudes, the bubble can continue to rise and grow, all the while condensing additional water vapor into cloud droplets and releasing yet more latent heat. If you have flown in an airplane through a big, cauliflower-shaped cloud, you have felt the turbulence created by these towers of rising air.

Latent heat is the main fuel that powers hurricanes, thunderstorms and normal bouts of lousy weather. The energy contained in latent heat is substantial; in a typical hurricane, the amount of heat energy released in one day is more than 200 times the energy in all the electricity produced worldwide per day. A hurricane can release the explosive power of a 10-megaton nuclear bomb about every 20 minutes.

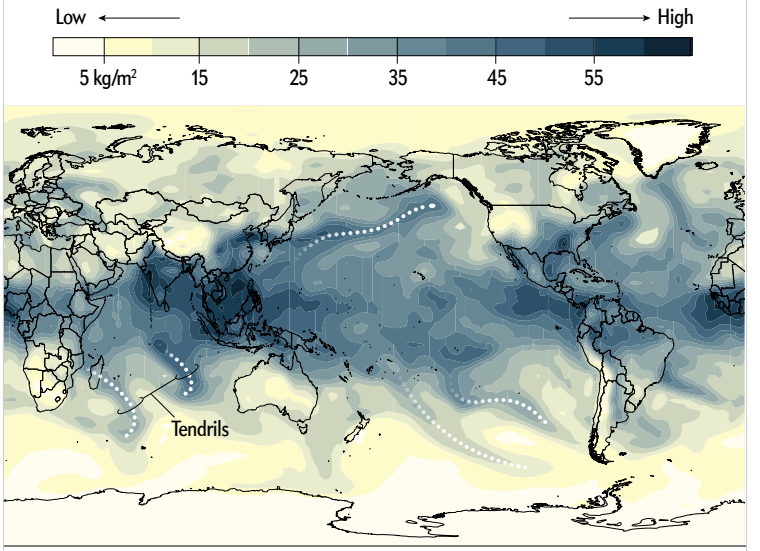
The most worrisome consequence of increasing atmospheric water vapor may be its role in the rapid intensification of tropical storms. Meteorologists say a storm has rapidly intensified when either the maximum wind speed increases by at least 30 knots (35 miles per hour) in a 24-hour period or the storm's central atmospheric pressure drops at least 42 millibars in 24 hours. In the past 40 years the probability that a storm will rapidly intensify in any

Wetter World

Atmospheric water vapor is distributed unevenly around the globe. It is generally heavy across the equatorial latitudes and lighter toward the poles, but storms and winds can pump tendrils of tropical moisture in those directions, too. The amount of airborne vapor overall is rising as the world warms, above oceans and even more so above land.

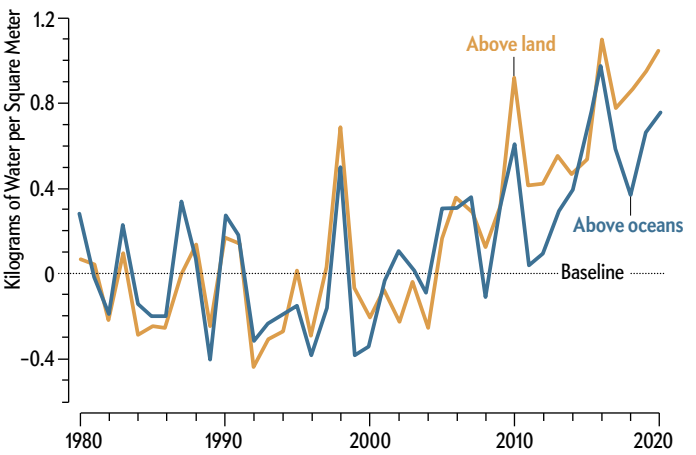
Water in the Atmosphere on August 31, 2021

Color indicates kilograms of water in a vertical column of atmosphere above a square meter of Earth's surface, if it all condensed and fell. Hurricane Ida's dark, circular signature is visible over the southeastern U.S.



Airborne Water Vapor on the Rise

In recent years the amount of vapor worldwide has increased above oceans and land compared with the annual average, or baseline, from 1981 to 2010.



Sources: NOAA/ESRL Physical Sciences Laboratory, Boulder, Colo, *http://psl.noaa.gov/* (*base map*); Web-Based Reanalysis Intercomparison Tool (NOAA/ESRL Physical Sciences Laboratory, NOAA Climate Program Office, and U.S. Department of Energy's Office of Science) *https://psl.noaa.gov/cgi-bin/data/testdap/timeseries.pl* (*chart base*); "The NCEP/NCAR Reanalysis 40-Year Project," by E. Kalnay et al., in *Bulletin of the American Meteorological Society*, Vol. 77; March 1996 (*data analysis model*)

Graphic by Jen Christiansen

HURRICANE IDA dropped 17 inches of rain on LaPlace, La., on August 29, 2021, and a resident walks through its floodwaters.

Luke Sharrett *Bloomberg* via Getty Images

given year has quintupled. In 2020 alone, 10 Atlantic hurricanes did just that: Hanna, Laura, Sally, Teddy, Gamma, Delta, Epsilon, Zeta, Eta and Iota. In 2021 five of the six Atlantic hurricanes that formed as of mid-September underwent rapid intensification, including Ida and Nicholas. Recent studies agree with physical common sense: rapid intensification becomes increasingly likely as oceans warm, evaporating more water and delivering more latent heat to the atmosphere. Oceans absorb about 90 percent of the heat trapped by extra greenhouse gases we humans have emitted. That heat raises water temperatures both at the surface and deeper below; the warm water acts like a powerful battery that storms can draw energy from.

Increasing water vapor is not the only impact of climate change on tropical storms, however. Decreasing wind shear—the difference in speed or direction between winds closer to the ground and those high in the atmosphere—also favors storm development because the towers of rising air are less likely to be torn apart. Other variables now being studied include changes in the amount of dust and pollution particles in the air, as well as differences in atmospheric warming at lower and higher altitudes, which affect how fast those bubbles of warm air rise.

For more than two decades much of the tropical North Atlantic Ocean has been abnormally warm, creating excess evaporation that fuels strong hurricanes. Nontropical storms are gorging on the atmosphere's extra vapor and energy, too, leading to more heavy-precipitation events and perhaps even heavier snowfalls.

DEADLY HEAT

THE THREAT FROM INCREASED WATER VAPOR extends beyond storms. It is also making summer nights intolerably steamy—more often and in more places.

Since the mid-1990s summer nighttime minimum temperatures over global land areas have been rising faster than daytime highs. That is because vapor is a greenhouse gas, and more of it means more warming: heat that would normally escape to space at night is instead trapped, preventing Earth's surface from cooling. And unlike carbon dioxide, which spreads worldwide regardless of where it is emitted, vapor tends to stay local.

More vapor also makes hot nights perilous. Higher nighttime humidity prevents your sweat from evaporating—the body's natural cooling system—leaving you to overheat and interfering with sleep. One measure of this discomfort is the heat index, which combines the effects of temperature and humidity to represent the stress one's body really feels. An index above about 100 degrees Fahrenheit (38 degrees Celsius) is considered dangerous; prolonged exposure can be fatal, especially to the elderly and infants. Heat stresses livestock and pets, too, and animals in the wild are adapting by moving toward higher latitudes or higher elevation if they can. Without a period of nighttime cooling, heat can also build up in soils, killing some plants and insects while allowing other, warmth-loving species to flourish. According to "A Declaration on Climate Change and Health 2021," published in August by a group of 32 health organizations, nighttime heat also heightens the risk of exposure to diseases carried by insects, threatening humans, animals and crops.

The danger posed by nighttime heat is growing not only for already hot tropical countries but also for those well north and south of the equator. Cities along the U.S. Gulf Coast have already exceeded the unsafe threshold many times. Warming in Houston has risen more than 3.5 degrees F (two degrees C) since 1970 because of the city's proximity to the Gulf of Mexico and its relentlessly expanding development, which is augmenting the urban heat-island effect. In July 2020 Houston's heat index topped 110 degrees F (43 degrees C), well beyond miserable.

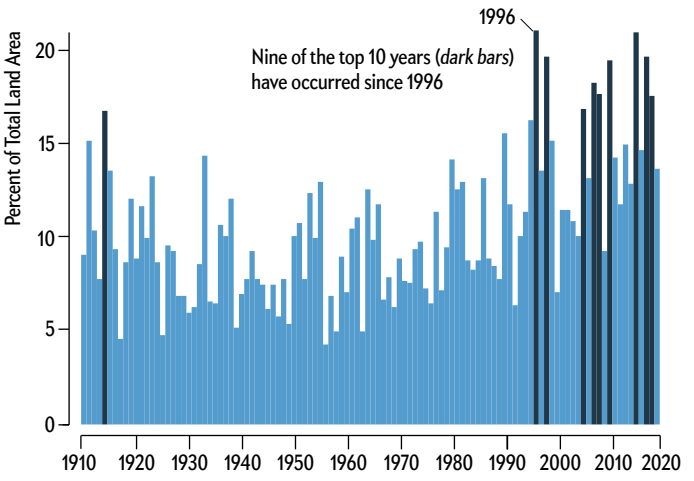
If greenhouse gases continue to accumulate in the atmosphere, these conditions will soon become commonplace in many southern and midlatitude cities such as Atlanta and Washington, D.C. Before 2000 the U.S. capital experienced an average of one night every five years with a minimum temperature above 80 degrees F (27 degrees C). Since 2000 these nights have occurred about twice a year—a 10-fold increase in just 20 years.

Yet certain countries in the tropics will suffer, and are already suffering, the most. In May 2015 a severe heat wave, perhaps better termed a "steam wave," hit India and Pakistan. Daytime heat indices exceeded 114.8 degrees F (46 degrees C) for several days, and the high humidity prevented nighttime cooling; more than 3,500 people succumbed to these stifling conditions. Add another half-degree of global warming and the number of people threatened by extreme heat will double to about 500 million worldwide.

Heavier Rains

Extreme rains and snows are happening more frequently, as warmer air and oceans generate more vapor in the atmosphere. An "extreme" storm delivers more precipitation in one event than 90 percent of a year's storms do. In recent decades these events have multiplied across many urban and rural areas and will increasingly become the norm.

Percent of U.S. Land Area* Where Extreme One-Day Rains or Snows Have Supplied Much More of the Annual Precipitation Than Average



**Contiguous 48 states*

Source: NOAA's 2021 U.S. Climate Extremes Index, via EPA's Climate Change Indicators in the United States *www.epa.gov/climate-indicators (data)*

Graphic by Jen Christiansen

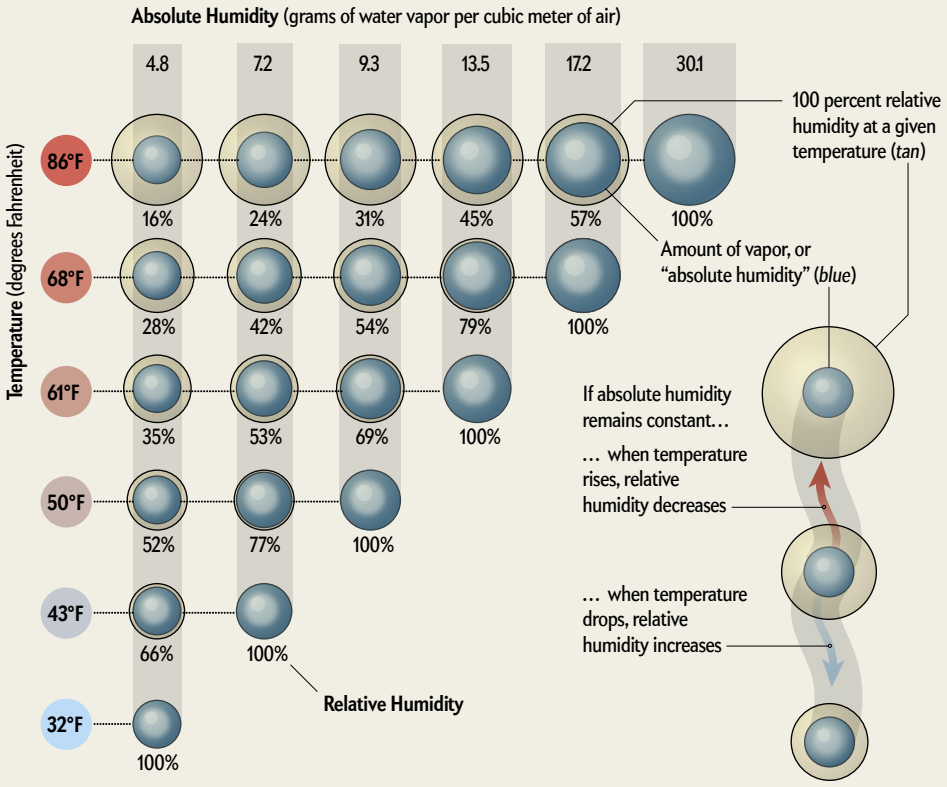
GLOBAL WARMING AMPLIFIER

IF INTENSE STORMS and sweltering nights are not troubling enough, water vapor is also making global warming worse. Even though carbon dioxide gets most of the attention, water vapor is by far the most important greenhouse gas in the atmosphere. It absorbs much more of the infrared energy radiated upward by Earth's surface than do other greenhouse gases, thereby trapping more heat. To put this into perspective, a doubling of atmospheric carbon dioxide concentrations *by itself* would warm the globe approximately one degree C. But feedback loops—vicious cycles—make the temperature rise twice as much. Again, although feedbacks such as disappearing sea ice get a lot of attention, the water-vapor feedback loop—warming causes evaporation, which traps heat, creating even more warming—is the strongest one in the climate system.

Perhaps counterintuitively, the water-vapor feedback is weakest where vapor is most abundant. In humid areas, the infrared energy absorbed by water vapor is already near its physical limit, so adding a little extra moisture has minimal effect. In dry places, however, such as polar regions and deserts, the amount of

What Is Humidity? It's Relative

Whether the air on a given day feels sticky or dry is a matter of relative humidity. In air at 32 degrees F (zero degrees C), water vapor can reach a maximum concentration of about 0.6 percent. At 86 degrees F (30 degrees C), the air can hold much more vapor—up to about 4.2 percent. When air at a certain temperature contains the maximum amount of vapor it can hold, its relative humidity (RH) is 100 percent.



infrared energy absorbed is well below its potential maximum, so any added vapor will trap more heat and increase temperatures in the lower atmosphere.

The rise in the number and duration of Arctic heat waves is a clear symptom of more frequent and longer-lasting pulses of warm, moist air from lower latitudes—those tendrils that extend northward from the tropics. In January 2021, for example, temperatures soared 36 degrees F (20 degrees C) higher than normal across large areas of the Arctic Ocean. Increasing Arctic heat waves, especially during winter, are slowing the annual freeze-up of sea ice and contributing to the demise of the ice cover.

Added vapor in the atmosphere helps tropical storms like Ida intensify faster, leaving precious little time for officials to warn people in the crosshairs.

The heat-trapping effect of additional vapor could perhaps be offset by an increase in cloud formation. Clouds reflect the sun's rays (leading to a cooling effect) but also trap heat. Over oceans the cooling effect tends to dominate, but the warming influence wins out at high latitudes. Recent studies suggest that on average over the entire globe, the heating effect is greater, establishing yet another vicious cycle involving water vapor.

BETTER FORECASTS

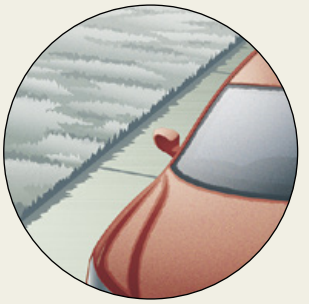
AS HUMAN ACTIVITIES CONTINUE to produce more heat-trapping gases, the oceans and atmosphere will continue to warm, and additional water will evaporate, leading to more frequent vapor storms and debilitating steam waves. Hurricanes in the strongest categories will occur more often, as will storms that intensify rapidly. Predicting these quick spin-ups will be a challenge for forecasters. When the storms intensify close to landfall, as Hurricane Ida did, officials will have precious little time to sound the alarm, and people will have mere hours to evacuate.

The main obstacle to predicting these overachieving storms is the lack of temperature measurements below the sea surface. A deep layer of warm water contains a lot more storm fuel than a shallow layer does, but satellites measure only ocean-surface temperatures. Researchers are trying to devise ways to determine how much energy is contained in the upper few hundred feet of ocean water because that is really what storms feed on. They are developing autonomous ocean gliders that

Graphic by Jen Christiansen

Clouds: We cannot see water vapor, but if more of it is added to air when the RH is 100 percent, a cloud will form. Clouds are simply the excess vapor condensing into small droplets of liquid water, which we *can* see. A cloud will also form if air with 100 percent RH cools. Clouds arise in many circumstances, such as when cold air with RH less than 100 percent blows from dry land over the ocean, where evaporation can raise the RH.

Fog: Fog is a cloud that sits on a land or water surface. When warm air moves over a cooler area—such as when a southerly wind blows over Maine's cold coastal waters—vapor condenses, creating fog. When warm air rises to a higher, cooler elevation—say, when winds blow up a mountain slope—fog or clouds can form. And after a warm day, when nighttime air radiates infrared energy to space, its temperature cools, and morning fog can form over fields and valleys.



Dew and Frost: Radiating heat on a clear, calm night can create dew or frost. Surfaces lose infrared heat more readily than the air does, so they cool faster. Water vapor in air that contacts a cooler surface can condense into droplets on grass—or freeze into crystals on lawns and car windshields if the temperature is cold enough.

Your Breath: When you exhale, your breath adds water vapor to the air. If you exhale enough vapor to raise the RH above 100 percent, it temporarily forms a little cloud, which soon dissipates as the tiny droplets evaporate. Because cooler air can hold less vapor, we tend to see our breath on colder days.

roam the upper ocean at different depths while sampling temperature and salinity. They are also working with data from satellites that can detect variations in the height of the sea surface: a deep layer of warm water expands relative to adjacent areas, creating a hump in the ocean surface that can be seen from space.

Satellite data are extremely valuable, but we also need instruments across the ocean that measure temperature, vapor and winds. We will continue to rely on "hurricane hunter" aircraft to fly into storms and drop instruments inside and around them. Researchers feed data from these flights into computer models that can provide details about the atmosphere's state and the storm's strength. Better data coverage, faster computers and greater understanding of storm-formation processes are helping to improve predictions.

Vapor arises from myriad sources and affects many atmospheric processes. Scientists do not completely understand some of the interactions, and computer models still struggle to fully predict the influences of water vapor in the changing climate system. Even the seemingly straightforward case of how fast water evaporates from an ocean or lake depends on many factors, such as the difference between the temperature of the water and that of the air just above it, how much vapor is already in the air, and wind speed. Over land the calculation is even more complex, involving additional variables such as how much moisture is in the soil and what types of plants are growing. Predicting what will happen to the vapor once it enters the atmosphere is yet another challenge. Will it condense into clouds, fuel a storm, and fall as rain or snow? Will it condense onto surfaces as dew or frost? Will it travel for hundreds, maybe thousands, of miles from the tropics to higher latitudes? Errors in any of these calculations will affect predictions of future temperature changes and weather patterns.

Increasing water vapor deserves more attention. Unfortunately, we cannot directly control the amount of it in the atmosphere. We can, however, reduce it indirectly by reining in the warming caused mainly by our emissions of carbon dioxide and methane, as well as by the clearing of trees that help to absorb carbon from the air. By reducing the warming rate, we can lessen the surge in vapor. If we succeed, we can slow the future intensification of vapor storms—and the havoc they can wreak. SA

FROM OUR ARCHIVES

A Shifting Band of Rain. Julian P. Sachs and Conor L. Myhrvold; March 2011.

scientificamerican.com/magazine/sa

Illustrations by Nick Bockelman

AGRICULTURE

THE POWER OF AGROECOLOGY

Farmers worldwide are growing and sharing food in ways that enhance nutrition, biodiversity and quality of life

By Raj Patel

Photographs by Thoko Chikondi

VILLAGERS IN BWABWA in northern Malawi share seeds, tips on cultivation, and the work of harvesting and carrying the produce home.

Raj Patel is a professor of public affairs at the University of Texas at Austin and a member of the International Panel of Experts on Sustainable Food Systems. His books include *Stuffed and Starved* and *The Value of Nothing*. Most recently, he co-directed with Zak Piper the award-winning documentary *The Ants & the Grasshopper*.

Although it is the sharp edge of the battle to end hunger, you could be forgiven for thinking you were watching a reality TV cooking show. Under the low peak of Bwabwa Mountain in Malawi, in a village on a tributary of the Rukuru River, about 100 people gather around pots and stoves. Children crowd around a large mortar, snickering at their fathers', uncles' and neighbors' ham-fisted attempts to pound soybeans into soy milk. At another station, a village elder is being schooled by a man half his age in the virtues of sweet potato doughnuts. At yet another, a woman teaches a neighbor how he might turn sorghum into a nutritious porridge. Supervising it all, with the skill of a chef, the energy of a children's entertainer and the resolve of a sergeant, is community organizer Anita Chitaya. After helping one group with a millet sponge loaf, she moves to share a tip about how mashed soy and red beans can be turned into patties by the eager young hands of children who would typically never volunteer to eat beans.

There is an air of playful competition. Indeed, it *is* a competition. At the end of the afternoon the food is shared, and there are prizes for both the best-tasting food (the doughnuts win hands down) and the food most likely to be added to folks' everyday diets (the porridge triumphs because although everyone likes deep-fried food, doughnuts are a pain to cook, and the oil is very expensive).

This is a Recipe Day in Bwabwa, a village of around 800 people in northern Malawi. These festivals are sociological experiments to reduce domestic inequality and are part of a multifaceted approach to ending hunger called agroecology. Academics describe it as a science, a practice and a social movement. Agroecology applies ecology and social science to the creation and management of sustainable food systems and involves 10 or more interconnected principles, ranging from the maintenance of soil health and biodiversity to the increase of gender and intergenerational equity. More than eight million farmer groups around the world are experimenting with it and finding that compared with conventional agriculture, agroecology is able to sequester more carbon in the soil, use water more frugally, reduce dependence on external inputs by recycling nutrients such as nitrogen and phosphorus, and promote, rather than ravage, biodiversity in the soil and on farms. And on every continent, research shows that farmers who adopt agroecology have greater food security, higher incomes, better health and lower levels of indebtedness.

Chitaya told me that at the turn of the millennium, when Bwabwa's farmers were still practicing conventional agriculture, "there were times when we wouldn't be able to eat for days. My first child was malnourished." Now her oldest son, France, is a very healthy adolescent, helping teach other boys how to cook. The pediatric malnutrition clinic near Bwabwa has closed down for want of cases—though in Malawi as a whole, more than a third of the children younger than five years are stunted by malnutrition. Despite the COVID-19 pandemic, whose devastating economic effects have deepened malnutrition across the world, agroecology continues to help Bwabwa evade hunger.

Yet when policy makers attended a United Nations Food Systems Summit in the fall of 2021, the solutions on the table for world hunger excluded agroecology. The summit's sponsors included the Gates Foundation, whose preferred solution is a set of technologies modeled on the Green Revolution. Despite a great deal of evidence that the Gates' Alliance for a Green Revolution in Africa has failed, one of its leading acolytes from Rwanda chaired the U.N. Summit. Advocates for agroecology, such as the Alliance for Food Sovereignty in Africa, which represents 200 million food producers and consumers, had too few resources to im-

WATER for drinking and cooking comes from a community tube well in Bwabwa. But climate change is causing water levels in the region to drop, often necessitating long treks to carry water home.

pact a process that increasingly silences their voices.

Ending hunger requires much more than pulling more food from the ground; it involves grappling with entrenched hierarchies of power. Over the past decade food production has generally outstripped demand—there is more food per person than there ever was. But because of global and regional inequalities, exacerbated by the recent pandemic, levels of hunger are higher now than in 2010. In other words, more food has accompanied *more* hunger. People are deprived of food not because it is scarce but because they lack the power to access it.

The global food system was originally established under colonialism, when the agriculture and land-ownership patterns of much of the tropical world were reconfigured, and tens of millions of enslaved and bonded laborers were shipped around the world to provide Europeans with cane sugar and other tropical crops for which they had developed a taste. Far from ending with colonialism, however, this system of food extraction has grown only stronger because of conditions attached to loans from international financial institutions such as the World Bank and the International Monetary Fund (IMF). To pay its debts, Africa now exports everything from roses to broth.

Agroecology frees the world's poorest farmers from such structures of control and shifts the balance of power in the global food system to people like Chitaya, one of billions who reside at the very bottom of the socioeconomic pyramid. Little wonder, then, that it is unpopular with conventional agricultural businesses, governments in the Global North and the organizers of the food systems summit. Its recognition that systemic problems require systemic solutions makes agroecology a threat.

HUNGER IN MALAWI

OVER A LIFETIME of trying to get to the bottom of why there is hunger and what might be done about it, I have traveled from within organizations like the U.N. and the World Bank to protest lines outside and within the World Trade Organization. During the past decade, however, I have also had a scientific education at the hands of some of the world's poorest farmers.

My first visit to Bwabwa was in 2011, at the invitation of my graduate school friend Rachel Bezner Kerr. Now a professor of development studies at Cornell University, Bezner Kerr had arrived in Malawi a decade earlier to find herself in the middle of an economic crisis. Malawi had suddenly reduced fertilizer subsidies—and that, too, while the HIV/AIDS pandemic was wreaking humanitarian and economic havoc. Farmers, most of whom practiced industrial agriculture, which requires expensive chemical inputs, were desperate. Bezner Kerr wanted to be of service as she developed a project for a

EXPERIMENTS with unfamiliar crops (*left*) and recipes have helped Bwabwa's villagers achieve healthy diets. So has gender equality, which reduces the burden on women. Winston Zgambo helps Anita Chitaya prepare bean-flour doughnuts (*center*). Her husband, Christopher Nyoni (*right*), also cooks, traditionally women's work.

master's degree, so she sought the most disadvantaged families to support in her research. She was lucky to meet Esther Lupafya, a nurse who headed the maternal and child health program at a clinic in the small town of Ekwendi. Together they identified farmers, including Chitaya, who were ready to try a different kind of agriculture—one that would free them from dependence on global agrobusiness and its allies.

Getting to Bwabwa involves a six-hour drive north from Malawi's capital, Lilongwe. Lined with signs heralding the projects of several nongovernmental organizations and foreign aid institutions, the northern road from the Lilongwe airport tracks the eastern shore of Lake Malawi, the continent's third-largest freshwater lake. After passing northern Malawi's biggest city, Mzuzu, with its six-story Bank of Malawi Building, and the smaller town of Ekwendeni, you follow dirt roads to reach Bwabwa. Whereas the large, flat, irrigated fields off the main highway are neat monocultures of corn, the fields near the village are drier, smaller, canted at every angle and packed with twirling thickets of different crops, each tailored to the needs of the family tending it and the capacity of that particular field's ecology.

Northern Malawi did not always look like this. The first white man to visit was Scottish Presbyterian David Livingstone in 1858. His missionary campaign led to the establishment of the British Central African Protectorate, which later became Nyasaland. Photographs from the time show scrubland. British agriculturist B. E. Lilley gazed on Malawi in the 1920s and declared: "The time has not arrived when the native can be looked to as a person who can be relied upon to raise produce to anything [like] the extent that the white man raises it." Similar attitudes persist to this day, though they are now couched in contemporary language.

Keen to wring what they could from the colony's resources, the British began to export ivory and forest products, moving on to the crops that would transform Malawi's land and economy: tea, cotton, sugar and tobacco. The colonists took over the land, but they needed workers, so they imposed a hut tax, an annual household fee payable in cash. Initially families paid the colonists by selling their stores of wealth, usually livestock, until there was nothing left to liquidate. Then they sent able-bodied men to sell their labor, in Malawian plantations and the mines farther south. Debt turned self-sufficient farmers and pastoralists into manual workers, laboring for a pittance.

Debt also turned Malawi into a pawn of its creditors. Malawi became independent in 1964, only to spend the next 30 years under autocrat Hastings Banda. Western donors rewarded his iron-fisted regime with high-dollar loans to support the country's industrial development while ignoring its worsening malnutrition. Such loans became the instruments of Malawi's, and in fact Africa's, hunger. In the early postcolonial period, Africa was a net food exporter, selling 1.3 million tons a year from 1966 to 1970. But the oil-price crisis of the 1970s forced African governments to borrow even more from the World Bank and the IMF. These so-called structural adjustment loans came with strict conditions that, among other measures, slashed public spending on education and health care and privatized national assets. Further, African countries were instructed to concentrate on exports of the colonial-era crops, which would earn the dollars with which they might repay their debts.

Despite paying an average of $100 million per year to its creditors throughout the 1980s, however, Malawi remains one of the most indebted countries on Earth. Worse, devoting the richest land to growing cash crops

for export, instead of food crops for subsistence, meant that structural adjustments had by the 1990s turned Africa into an importer of a quarter of its food. Between 2016 and 2018 Africa imported 85 percent of its food from outside the continent—a debilitating dependence.

TRIAL, REVIEW, EXCHANGE

IN 1992 A NATIONAL SURVEY revealed that 55 percent of Malawian children had failed to reach the appropriate height for their age—a key measure of malnutrition. The government tried to defy the austerity imposed by international banks and donors by subsidizing fertilizers for farmers but eventually caved to their demands to instead prioritize paying off the loans. Lupafya and Bezner Kerr began their work soon after these supports were removed, establishing the Soils, Food and Healthy Communities (SFHC) initiative in Ekwendi in 2000. Starting with 30 farmers, the SFHC now works with more than 6,000 people across 200 villages to promote agroecology.

Along with Chitaya and others, the women began with a round of experiments, intercropping local groundnuts and other legumes. This double-legume system allowed the farmers to harvest nuts and beans for their children and then dig the nitrogen-rich residue back into the soil to boost maize production—without buying fertilizer. Some farmers went further, experimenting with vegetable intercropping patterns. Simultaneously, the SFHC developed a system of peer review, in which the participants met regularly to discuss measures to improve soil fertility. Women farmers had long been exchanging seeds and knowledge to grow finger millet, a drought-tolerant plant that produces highly nutritious grains that make for hearty porridge and, if you can stomach it, sour beer. The SFHC formalized this tradition of evaluating and sharing information.

By running trials of different legume cropping systems in a "mother" location in the middle of different villages, farmers could then adopt "baby" trials in their own fields based on their preferences for soil health, nutrition and the time they could spare to tend the crops. Through discussions and iterations over the years, initial trials grew from a few dozen households to reach thousands of farmers, with a pigeon-pea-and-groundnut combination proving to be the most successful in fixing nitrogen. As the soil improved, some farmers, many of them women, did well enough not only to feed their families but also to sell a respectable surplus at the local market.

Still, every farmer, every field and every season are different, so the experiments continued. Some women tried seemingly incongruous combinations such as soy and tomatoes—originating in Asia and the Americas, respectively—alongside indigenous African varieties such as finger millet. (Millet cultivation had earlier been discouraged because the grain could not be exported for dollars, but it persisted because women often brew it into beer as a means of earning extra income.) In Bwabwa, the fields are a mixture of foreign and native varieties, selected through trial and obser-

What Is Agroecology?

Agroecology is a way of producing food that mimics nature, using biodiversity and the recycling of resources and nutrients to increase productivity, control pests, eliminate chemical inputs and enrich soils. Just as important, it enables marginalized communities not only to produce enough food for themselves and others in a sustainable way but also to ensure that it is distributed fairly, enhancing nutrition and gender, intergenerational and other forms of equity. The U.N.'s Food and Agriculture Organization has identified 10 key principles that communities pursuing agroecology follow.

Recycling

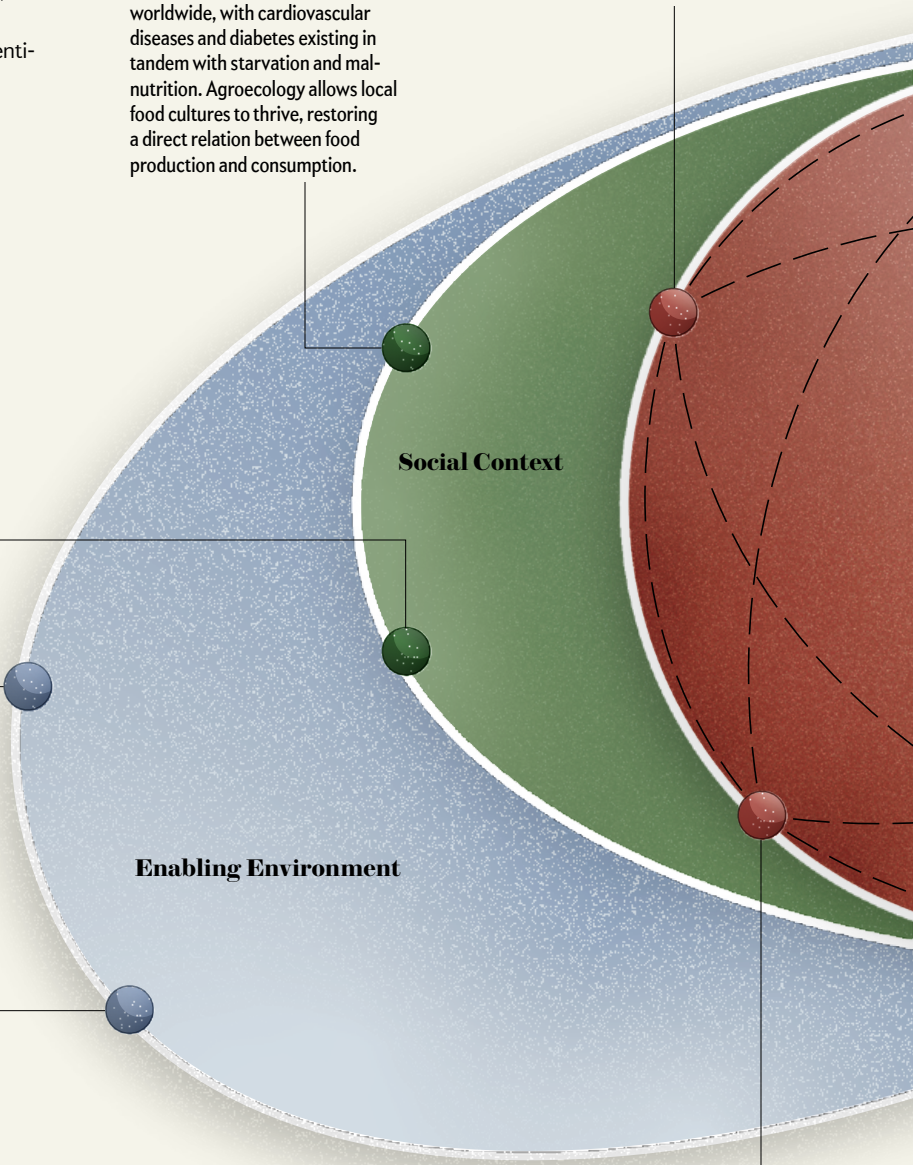
Agroecology recycles natural resources and nutrients. Like nature, it produces no waste. In recurring cycles, atmospheric nitrogen moves into the soil and back, rainwater travels from grove to field to air, manure from farm animals provides fertilizer and crop residues such as straw become livestock feed.

Culture and Food Traditions

Industrial agriculture and global trade have generated imbalanced diets worldwide, with cardiovascular diseases and diabetes existing in tandem with starvation and malnutrition. Agroecology allows local food cultures to thrive, restoring a direct relation between food production and consumption.

Human and Social Values

Attention to equity, inclusion and justice ensures that no one goes hungry. Women, who in most cultures are responsible for feeding the family, are among the key innovators and leaders of agroecology projects. Whereas industrial systems devalue farm labor, food production becomes an enjoyable, shared task and a vehicle for enhancing ties with nature and the community. Protecting the environment enables future generations to inherit intact natural systems.



Circular and Solidarity Economy

Agroecology seeks to link producers and consumers of food in local circles, so that production is directly tied to need. Such localized economies boost the incomes of food producers, provide consumers with fresher produce, foster community ties, and reduce food waste and energy use in transportation.

Responsible Governance

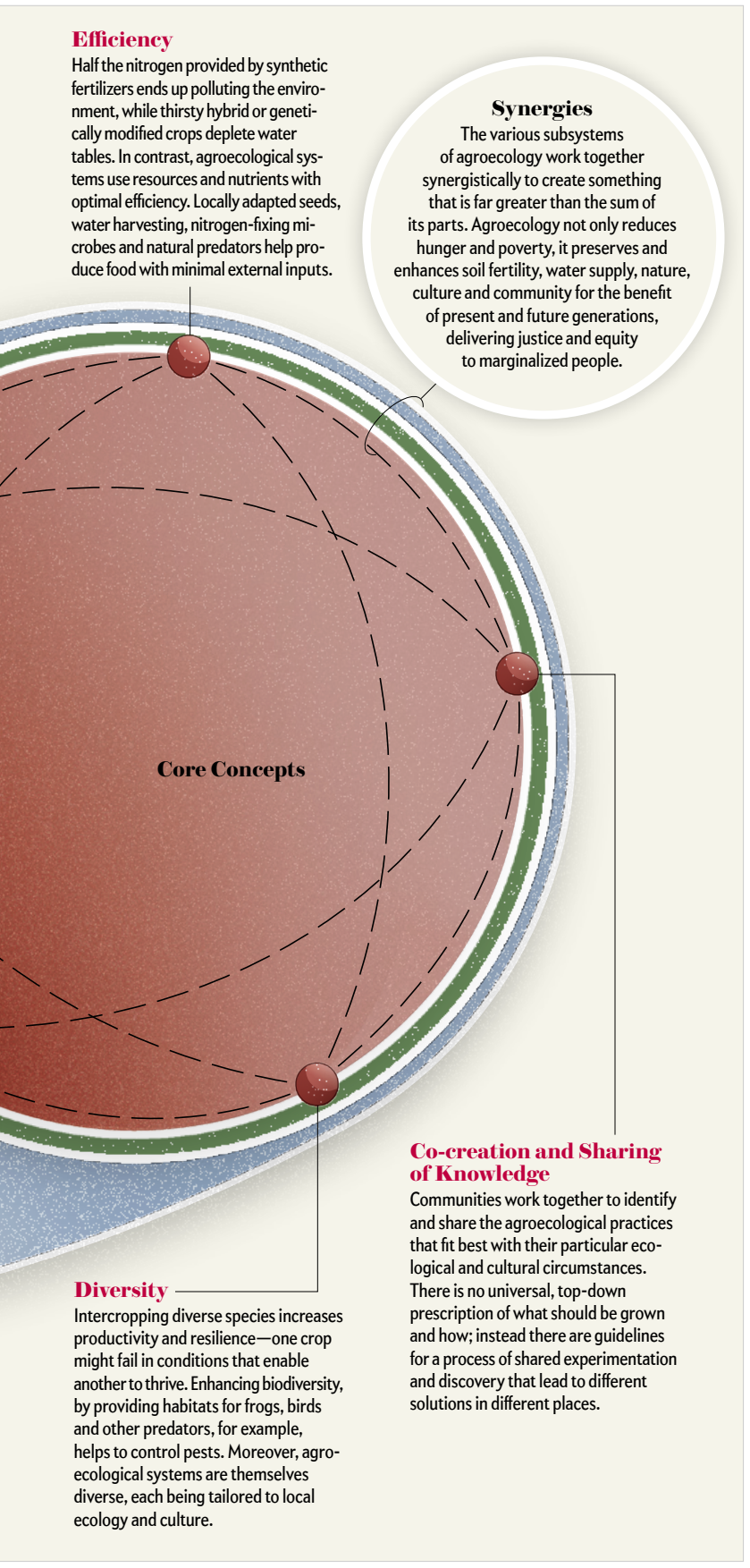
Systems of governance at global, national and local levels that protect the rights of food-growing communities to land, clean water, intellectual property (such as traditional seeds and know-how) and other resources are essential for agroecological systems to thrive. Existing systems of trade and governance militate against the well-being of small farmers, who are among the hungriest and most indebted people in the world.

Resilience

Crop diversity ensures quicker recovery from climate-related disasters and other natural exigencies. In addition, the ability to grow food with local and recycled inputs helps to insulate communities from external economic shocks.

Source: The 10 Elements of Agroecology: Guiding the Transition to Sustainable Food and Agricultural Systems, Food and Agriculture Organization of the United Nations, 2018 (*reference*)

Graphic by Federica Fragapane



vation, with networks of farmers exchanging knowledge and ideas and reviewing one another's work.

That openness to experimentation and adaptation explains why, around March, it is possible to see in the unpromising red soil a cultivation system that looks like it may not belong. Tall rows of corn burst from the ground. Twirling around them are pole beans, and at their feet are the fat, dark fan-shaped leaves of local pumpkin, together with their blossoms. In Mesoamerican agriculture, this kind of technique is known as the three sisters: corn, beans and squash.

In Malawi, locally adapted varieties work together in similar ways: the corn or millet provides the starchy cereal that forms the backbone of every meal. The stalks also scaffold the beans, which yield protein and fix nitrogen. Root nodules in legumes (such as beans and groundnuts) are a site of symbiosis between the plant and rhizobia bacteria. The plant provides the bacteria with energy; the bacteria take nonreactive nitrogen molecules from the air and turn them into ammonia and amino acids for the host. This works well for cereals, which need bioavailable nitrogen to do well. The pumpkin (or other squash) provides big leaves for shading out weeds, and its flowers attract beneficial insects that keep pest pressure down. Plus, at the end of the season, there are gourds.

When put together, these crops produce more food per unit area than when they grow alone. Polycultures are demonstrably more abundant than monocultures. After harvest, the crop residue is reincorporated into the soil to build fertility and structure for the soil's biome.

In the early 2000s, as soil fertility in Bwabwa improved, some of the poorest women began to harvest an abundance of cereal, beans and vegetables. Interest in the cropping techniques spread. But despite real improvements in food production, child malnutrition remained puzzlingly high. Some of the farmers in the project, excited that they were becoming agronomists, started to wonder how to tackle the problem more directly. As they would discover, they had made progress in freeing themselves from external structures of power—but had yet to tackle internal ones.

WRESTLING DOWN PATRIARCHY

THROUGH HER WORK at the pediatric clinic, Lupafya had formed a suspicion: tradition was partly to blame for infant malnutrition. Ethnographic research across the SFHC villages confirmed her hunch. Within the patriarchal extended family, mothers-in-law have authority over their daughters-in-law. When an ill-founded parenting tip—that children cry because they are not being given solid food—is propagated through these networks, young mothers often find themselves counseled to wean their children at the age of two months. This advice runs counter to overwhelming scientific evidence that exclusive breastfeeding for six months and then a mix of breast and solid food until two years of age offer children the best start in life.

Lupafya crafted a way to walk the tightrope of respectful disagreement. The SFHC trained village wom-

en and men as facilitators to broker difficult conversations, particularly those between mothers- and daughters-in-law. Through monthly meetings and leadership from Lupafya and others, the science spread, and the misinformation was dispelled.

Lupafya learned something as well. "Change begins with denial," she told me. "It is the one who debates the most who will change." Having tackled the availability of food and breastfeeding practices, the grassroots social scientists moved to another determinant of infant malnutrition they had identified: domestic violence and, more broadly, patriarchy. Women's autonomy is linked with improved child nutrition indicators. As they observed, gender inequality meant that mothers had to spend time cooking, cleaning, managing the farm *and* breastfeeding. To have men help in domestic labor would increase women's autonomy. The question was: How do you get men to cook?

To find out how this transformative change happened, I worked with the SFHC team for more than a decade, documenting Chitaya's work in a film called *The Ants & the Grasshopper*. Chitaya had first met Lupafya when she visited the pediatric nutrition clinic. The older woman, Mama Lupafya as she is called, had supported her in a difficult marriage, one into which Chitaya had been coerced. Through attending workshops hosted by the SFHC, then by finding work as one of its trainers, and through long and difficult work in her home, Chitaya has transformed her marriage into one characterized by equality.

There are times when her husband, Christopher Nyoni, struggles to pull his weight in the house. He is afflicted by night blindness, a possible consequence of his own malnutrition early in life. When it gets dark, he is no longer able to cook or clean and needs help finding his way around the house. But by the light of day, he can be seen hunched over a stove or doing laundry or fetching water—all of which are traditionally women's work. It is a sign of Chitaya's success that Nyoni is keen to break with patriarchal tradition: "I do not want my son to get married the way I did," he told me.

The pathway to transforming this and other gender relationships in Bwabwa lay through changing the culture around food. An initial effort to achieve this shift involved door-to-door organizing. Members of the SFHC would visit households with an expert and offer to teach men how to cook novel foods, such as soy. After an enthusiastic afternoon gathered around a stove, surrounded by exhortations to do better, the men promised they would change. They did not. So the SFHC farmers brainstormed an alternative.

A constant worry for men was the social stigma of doing the effeminate work of cooking. "What if my friends see me?" asked Winston Zgambo. Having tried to cater to men's embarrassment by offering private cooking lessons, the SFHC team tried the opposite. They held public cooking competitions for whole families. On Recipe Days, all men were involved in cooking—and it was fun. By gamifying the change in behavior through offering prizes and social recognition for success, the women cracked open the possibilities for changing not just food culture, but inequalities in power within the home.

Data from the SFHC's work speak for themselves. Participation in the program moved children from being below the average weight for their age to surpassing the average. A recent study in which women farmers showed other mothers how to farm led to a range of benefits, from increased dietary diversity for children to lower maternal depression rates and higher rates of fathers' participation in chores.

NUTRITIOUS FOODS such as pigeon peas and beans (*left*) are typically not children's favorites, but teaching them to cook helps shape their tastes (*center*). Deep-fried bean-flour doughnuts (*right*) are always welcome.

A TEEMING FUTURE

AGROECOLOGY MEANS TAKING CARE not just of all humans but also of the ecosystems on which we depend. Under chemical agriculture, farmers grow a single crop. They buy fertilizers, pesticides, herbicides and access to water, and if necessary, they rent pollinators to maximize the yield. They use the revenue from selling the harvest to pay their bills and debts. In agroecology, farmers find ways not to exterminate pests but to reach an ecological equilibrium. They accept a little crop loss while providing habitats for predators and introducing other forms of biological control to obtain a much more robust and resilient ecosystem. In northern Malawi, biodiversity is part of the SFHC's success, as it is in every successful agroecological system. There are more insects, amphibians, reptiles, fish, birds and mammals in these landscapes than in the barren green deserts of modern monoculture.

In a world of extreme weather, agroecological diversity—both social and biological—is a source of resilience. When Hurricane Ike ploughed through Cuba in September 2008, it left trees and debris littering the fields. In Sancti Spíritus province, researchers noticed that the farms that followed the principles of conventional agriculture, with vast expanses of the same kind of crop, took around six months to recover from the devastation. But the most diversified farms, with tall plantains, fruit trees, perennial crops and ground cover, were able to recover 80 percent of their prestorm capacity in just two months. With high canopy trees blown over, more light fell on other plants in the understory, which grew faster: the diversity constituted a kind of botanical insurance portfolio. Moreover, families living on diversified farms could save some trees the morning after the storm, when conventional farm workers were far from the fields where their labor was seasonally contracted.

Agroecology also enables income resilience. Small farmers typically receive very little support. Instead they need to manage the flows of cash around the farm themselves. Conventional agriculture has one big burst of cash at harvest time, which may or may not be enough to pay off farming-related debts and dwindles throughout the year. With agroecology, on the other hand, income streams can be augmented by means of crops that mature in the leanest times. In Mexico, for instance, one group of farmers supplements its corn income with countercyclical honey and coffee harvests.

In the absence of reliable banks, farmers have sometimes turned to creating their own circular economies and exchanges. Many places have local grain stores that help to manage the booms and busts in harvests and hunger. In Bwabwa a few years ago women set up a credit circle to help manage cash flow and to develop other income streams, such as the sale of "climate change stoves," cooking stands that require much less wood than conventional wood-burning methods. A dozen women pooled their resources and took turns borrowing the cash and then repaying it. But the savings circle was wiped out in the IMF-mandated devaluation of the Malawian kwacha (currency) in 2012.

The COVID-19 crisis has made farmers' lives harder. Rising food prices have strained finances, and with resources diverted to emergency mitigation measures so that communities could stay home and stay safe, everyone's life has become harder. Yet agroecological practices appear to have enabled the SFHC's villages to endure the pandemic better than communities outside the project.

FEED THE WORLD

WHAT HAPPENS IN MALAWI and among the hundreds of millions of farmers experimenting with new kinds of

agroecology matters for the planet. Agroecology offers the ability to do what governments, corporations and aid agencies have failed to do: end hunger. For a while, it might have been easy to respond to agroecology by saying "that's all very nice, but it won't feed the world." But farming families that engage in agroecology have improved indicators of income and nutrition. From Nepal to the Netherlands, when agroecology is not confined to the field but extends into the home with equality and into community networks of exchange and care, farmers are financially and physically better off.

With ideas from the World Economic Forum and with support from the food and chemicals industry, the solutions on the table at the U.N. meeting were far less imaginative. Nor did they go far enough to remedy or even acknowledge the environmental and other harms committed by industrial agriculture. This supposedly scientific method of growing food is one of the largest drivers of climate change. Algae blooms from nitrogen and phosphate pollution are devastating aquatic life. Pristine forests are falling to ranches and plantations. Aquifers are being drained for thirsty cash crops. Fertile soil is turning to sterile dust as synthetic chemicals kill essential microbes, and pesticides are decimating insects on which extended chains of life depend.

This past July the Rockefeller Foundation reported that whereas Americans spent $1.1 trillion on food in 2019, the additional external health, environmental, climate change, biodiversity and economic costs associated with the food industry were $2.1 trillion. That is quite a debt—and one that the industry will never have to pay. The rest of the world shoulders the cost. Yet the firms behind this damage were the ones offering solutions at the summit.

We know how to do better. Agroecology more than fits the bill—not only because the crops grown are more diverse but because the social arrangements that surround them are more cognizant of power. Industrial agriculture's hidden costs are precisely the ones agroecology makes explicit. Its pathways reward the acumen of those on the front lines, support the livelihoods of the poor and protect the biodiversity of the planet. Its researchers and practitioners are already hard at work, teaching and learning from one another.

Such networks of knowledge undo the colonial savior complexes to which many development experts are still tied. Instead, under agroecology, as Chitaya puts it, "women can teach men, Black people can teach white people, the poor can teach the rich." She reflects on the certainties of struggle ahead, particularly as the powerful seem to be doubling down on industrial agriculture. "So much has been lost. But it's never too late to change." SA

FROM OUR ARCHIVES

Restoring Rice Biodiversity. Debal Deb; October 2019.

scientificamerican.com/magazine/sa

ABUNDANCE—of food, comradeship, equality, resilience and joy—is among the harvests of agroecology.

BABOON MUMMY found in tomb KV 51 in Egypt's Valley of the Kings is thought to preserve a beloved royal pet.

PRIMATOLOGY

Secrets of the Sacred Baboons

Studies of living and mummified baboons hint at why ancient Egyptians revered these pesky primates and reveal the probable location of a fabled kingdom

By Nathaniel J. Dominy

Richard Barnes

IN THE COLLECTIONS OF THE BRITISH MUSEUM IN London, a mummy known simply as EA6736 sits in eternal repose. Recovered from the Temple of Khons in Luxor, Egypt, it dates to the New Kingdom period, from 1550 B.C. to 1069 B.C. Clues to the identity of EA6736 emerge after close inspection. Its painstakingly wrapped linen bandages have disintegrated in some places, revealing fur underneath. Stout toenails poke out from the bandages around the feet. And x-ray imaging has revealed the distinctive skeleton and long-snouted skull of a primate. The mummified creature is *Papio hamadryas,* the sacred baboon.

Trustees of the British Museum

EA6736 is just one of many examples of baboons in the art and religion of ancient Egypt. Appearing in scores of paintings, reliefs, statues and jewelry, baboons are a recurring motif across 3,000 years of Egyptian history. A statue of a hamadryas baboon inscribed with King Narmer's name dates to between 3150 B.C. and 3100 B.C.; Tutankhamun, who ruled from 1332 B.C. to 1323 B.C., had a necklace decorated with baboons shown adoring the sun, and a painting on the western wall of his tomb depicts 12 baboons thought to represent the different hours of the night.

Egyptians venerated the hamadryas baboon as one embodiment of Thoth, god of the moon and of wisdom and adviser to Ra, god of the sun. The baboon is not the only animal they revered in this way. The jackal is associated with Anubis, god of death; the falcon with Horus, god of the sky; the hippopotamus with Taweret, goddess of fertility. Still, the baboon is a very curious choice. For one thing, most people who routinely encounter baboons regard them as dangerous pests. For another, it is the only animal in the Egyptian pantheon that is not native to Egypt.

Archaeologists have long puzzled over the prominence of the hamadryas baboon in ancient Egyptian culture. In recent years my colleagues and I have made some discoveries that bear on this mystery. Our work points to a biological explanation for the deification of the species. It also shows how the Egyptians obtained these exotic animals. Intriguingly, our insights into the sourcing of sacred baboons illuminate another enduring enigma: the likely location of the fabled kingdom of Punt.

Nathaniel J. Dominy is a primatologist and evolutionary biologist at Dartmouth College. His research focuses on primate ecology, behavior and functional morphology.

AN ODD GOD

"BABOONS!" is an unwelcome cry at any six-year-old's birthday party. My family was living in Kenya when a troop of 20 baboons swaggered into our backyard, causing a great scattering of shrieking children. The invaders headed straight for the food table, which was neatly adorned with cupcakes, sliced fruit and juice boxes. They won the carb lottery that day, taking just minutes

MUMMIFIED baboon EA6736 (*left*), recovered from the Temple of Khons in Luxor, Egypt, and a necklace belonging to Tutankhamun (*right*) are some of the many examples of hamadryas baboons depicted in ancient Egyptian art and religion.

Nathaniel J. Dominy

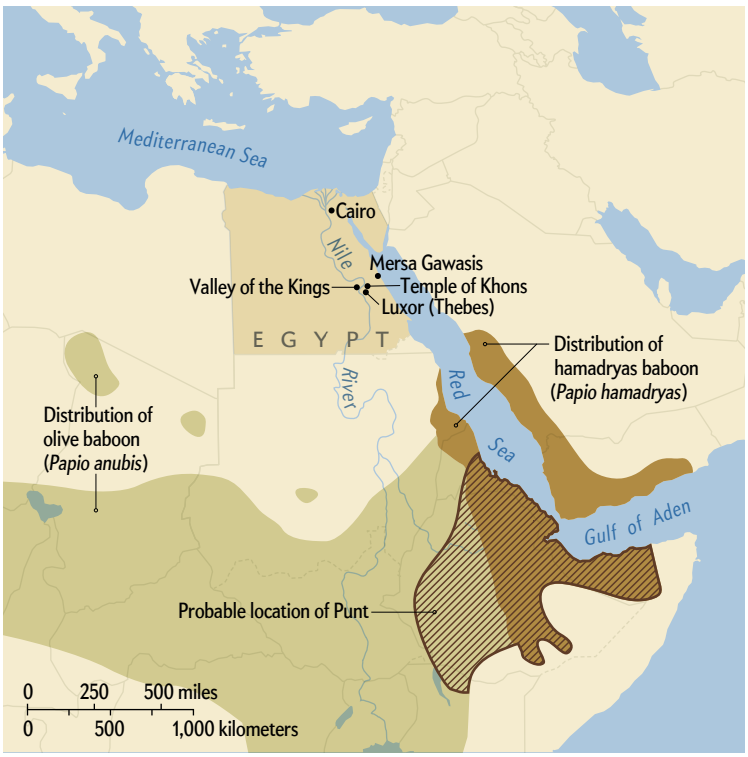
to fortify themselves with hours' worth of human labor. Setting aside my son's tears, the worst of it was watching the two males as they yawned in my direction. As a primatologist, I know that yawns are a pointed social signal, a way to advertise razor-sharp canine teeth that can cut a human limb to the bone with a single bite. In this context, however, the yawns seemed to convey not intimidation but full-bellied smugness.

When I recounted this tale to my Kenyan colleagues, it elicited knowing nods and a proverb: "Not all baboons that enter a maize field come out satisfied." Like many African proverbs, this one is layered with meaning. It alludes to the monkeys' insatiable crop raiding while simultaneously evoking sinister intent. Catherine M. Hill, a professor of anthropology at Oxford Brookes University in England, has found that baboons exact a devastating toll, reducing crop yields by half for some families in western Uganda. Indeed, baboons are the foremost pest for many subsistence farmers in Africa, and cultural aversions to the animals run deep. If erasure is the ultimate measure of contempt, then it is telling that in the art and handicraft traditions of sub-Saharan Africa, baboons are largely absent. This history makes the ancient Egyptians' worship of this creature—and its ubiquity in their art—deeply perplexing.

It is worth noting that modern baboons are typically divided into six species. All are native to sub-Saharan Africa and southwestern Arabia, and most people view them as pests. Researchers know from archaeological remains that the ancient Egyptians imported both *Papio anubis,* commonly known as the olive baboon, and *P. hamadryas*. But they deified only the hamadryas baboons, so any explanation for why the Egyptians revered baboons must account for their devotion to one species and not the other.

In their efforts to decode the significance of the hamadryas baboon, scholars have considered the way it is depicted in Egyptian art, noting two iconic forms. In the first, a male baboon sits on the thickened skin of its buttocks with its hands on its knees, its tail curled to the right and a disk representing the moon placed

Sandro Vannini



Map by Dolly Holmes

over its head. In the second, termed the gesture of adoration, the male baboon's arms are raised with palms upturned toward Ra, the sun god. Numerous Egyptian texts link baboons to Ra. For example, the ancient funerary texts known as the Pyramid Texts describe the baboon as the oldest or most beloved son of Ra. The Egyptian Book of the Dead explains that a suitable pronouncement of a deceased and newly resurrected person is, "I have sung and praised the Sun-disc. I have joined the baboons, and I am one of them."

To explain this connection between baboons and Ra, Egyptologist Elizabeth Thomas suggested in 1979 that the ancient Egyptians could have seen baboons face the rising sun to warm themselves and interpreted the behavior as their welcoming the sun. Her idea got a big boost a decade later, when the late Herman te Velde, another Egyptologist, elaborated on it by emphasizing the accompanying vocal behaviors of baboons, which he believed could have been taken as verbal greetings to the sun. Texts from the Karnak temple complex near Luxor describe baboons as "announcing" Ra while "they dance for him, jump gaily for him, sing praises for him, and shout out for him." In te Velde's view, people probably thought baboons were sacred because they seemed to communicate directly with Ra. The Egyptians saw the jubilance and inscrutable language of baboons as evidence of religious knowledge, he surmised.

Thomas's and te Velde's notions about what attracted Egyptians to these animals are fascinating, but are they plausible? Do baboons actually pay special attention to the morning sun? And are hamadryas baboons distinctive in this regard? Neither Thomas nor te Velde had much knowledge of primate behavior, and no primatologist had evaluated their ideas. Recently, however, findings bearing on these questions have emerged.

Many animals bask in the sun, an activity most biologists view as a way to minimize the energy cost of

WALL PAINTING in Theban Tomb No. 100, which dates to around 1479 B.C. to 1425 B.C., depicts in the top row of figures a procession from Nubia marching with a hamadryas baboon, among other exotic goods (*above*). Such luxury items were imported from the kingdom of Punt, which new research suggests was located in the southern Red Sea region (*map*).

rewarming the body after a cold night. The ring-tailed lemurs of Madagascar, for instance, often face the morning sun in a posture resembling the lotus position of yoga but with extended legs. The late primatologist Alison Jolly once noted that Malagasy legend describes lemurs as worshiping the sun, holding their arms out in prayer. In 2016 Elizabeth Kelley, executive director of the Saint Louis Zoo's WildCare Institute, found that sun basking in these primates was strongly correlated with low overnight temperatures. Kelley and her colleagues also discovered that the skin of the chest and abdomen in these lemurs contains more melanin than the skin on the back, a reversal of the prevailing mammalian skin-color pattern. Melanin is a light-absorbing pigment, and greater amounts in the abdominal area facilitate not only warming but also digestion.

Primate studies carried out over the past few years indicate that baboons reap similar digestive benefits from soaking up the sun. The microbes that live in primate intestines are vital to the digestion of plant matter. A rising body temperature spurs microbe activity, which in turn increases the intestines' absorption of nutrients. Thus, sun basking is a simple and effective way for animals to jump-start their microbes in the morning. The benefits are twofold. First, digestion itself generates heat—good for warming a body chilled by the night air. Second, if a cold night slowed digestion during sleep, then it is both efficient and prudent for a primate to finish digesting yesterday's meal before searching for a new one.

It stands to reason, then, that some primate species should bask in the sun more than others, depending on where they live and what they eat. Hamadryas baboons live in arid habitats across the Horn of Africa and parts of Arabia. The western edge of their geographic range meets the eastern edge of the range of *P. anubis* in the Awash River Valley of Ethiopia, a setting that has long invited comparisons of ecological and behavioral differences between the two baboon species. Feeding observations reveal that hamadryas baboons eat more leafy plant tissues than olive baboons do, which means their diet is higher in fiber.

In theory, given their distinct diets, hamadryas and olive baboons should differ in the abundance and types of microbes they need to digest plant foods. Recent studies of the gut microbiomes of the two species conducted by biological anthropologist Steven Leigh of the University of Colorado Boulder and his collaborators, including me, bear this prediction out. We found that the hamadryas baboon has more so-called cellulolytic microbes—which break down plant cell walls—than the olive baboon does, in keeping with its higher-fiber diet. The upshot of these findings is that the hamadryas baboon appears to have more to gain from early-morning sunbathing than the olive baboon has.

Our gut microbiome findings corroborate Thomas's hypothesis that Egyptians witnessed hamadryas baboons "welcoming the sun-disc." They may also explain why Egyptians venerated *P. hamadryas* over *P. anubis:* perhaps its dietary ecology produced morning behaviors that resonated more strongly with their religious beliefs.

A LOST LAND

WHATEVER THE REASON for their devotion to this species, ancient Egyptians went to great lengths to acquire living hamadryas baboons. Their demand for these animals, as well as for other luxury goods, including gold, incense and ivory, became a market force that shaped the course of world history.

In 1906 Theodore M. Davis, a colorful American lawyer and financier, discovered five mummies of *P. hamadryas* in the Valley of the Kings. The mummies came from tombs attributed to either Amenhotep II or King Horemheb, both of whom were members of the first dynasty of the New Kingdom, a period of great prosperity. The tomb of Amenhotep II's father, Thutmose III, contained a *P. hamadryas* skull that had apparently been unwrapped and then jettisoned by discriminating tomb raiders. Although baboons are depicted in older Egyptian art, these mummies represent the earliest-known physical remains of hamadryas baboons in Egypt. The abrupt appearance of *P. hamadryas* in these funerary contexts suggests that it was imported at great expense. Salima Ikram, a professor of Egyptology at the American University in Cairo, has argued that these baboons were cherished pets as well as exotic status symbols. Their presence in royal tombs and the high quality of their mummification—using prodigious lengths of the finest linen—speak to their value. Only the wealthiest Egyptians could afford this superior means of preserving bodies for the afterlife.

To determine where ancient Egyptians got their hamadryas baboons, my colleagues and I analyzed two mummies, one of which was EA6736. Both specimens had been purchased by Henry Salt, British consul general in Egypt from 1816 to 1827, and were later acquired by the British Museum. Although the ages of these mummies are not known as precisely as those of Davis's mummies, considering their style of wrapping and the fact that they came from Theban temples, they were probably mummified during the New Kingdom period.

Texts and inscriptions from this time indicate that the Egyptians used their port at Mersa Gawasis to conduct maritime expeditions to the mysterious kingdom of Punt, a faraway realm of luxury goods that was said to exist "in God's land." The global historical importance of Punt is considerable. British historian John Keay described the sea route to Punt as the first long step in the spice route, a trade network that drove maritime technologies and shaped geopolitical fortunes for millennia. But there is a problem, as archaeologist Jacke Phillips observed in 1997: "Punt has not yet been located with certainty on any map, and no archaeological remains have ever been identified, even tentatively, as 'Puntite.'"

If Egyptians obtained hamadryas baboons from Punt, then tracing the geographic origins of the mummies more specifically might allow us to pinpoint the location of this legendary place.

Luckily, we can reconstruct the lifetime movements of the baboons that were mummified by examining the chemical compositions of their tissues. My colleagues and I focused on the element strontium because its composition in bedrock differs from place to place. The strontium is absorbed by the surrounding soil and water and enters the food chain when animals eat plants that grow in the soil and drink the local water. Strontium in an individual's teeth, which develop early, can thus reveal where it was born; strontium in bone and hair, which change throughout life, can show where it lived just prior to death.

We compared the strontium compositions of the mummies' bones and teeth with those of baboons living in various regions across Africa. Our spatial analysis of these chemical profiles indicates that the animals were born outside Egypt in the southern Red Sea region, which encompasses the modern-day countries of Ethiopia, Eritrea, Djibouti and Somalia. Gratifyingly, historians have previously highlighted these areas as potential locations for Punt on the basis of written accounts, as well as images of plants and animals on the walls of Egyptian temples and tombs. A great strength of our result is that it puts Punt within the natural distribution of *P. hamadryas*.

The revelation that baboons were imported alive from the southern tip of the Red Sea is a testament to the astounding reach of Egyptian mariners during the second millennium B.C., demonstrating that they could sail at least 1,300 kilometers each way in open boats without a keel or rudder. It must have been a treacherous journey, and it is perhaps no accident that one of the most famous narratives in Egyptian literature is *The Tale of the Shipwrecked Sailor,* which tells the story of an Egyptian sailor who washes ashore on a magical island in the Red Sea.

We still have much to learn about ancient Egyptian religious beliefs and trading practices. As we move forward, it would be useful to examine the morning behaviors and melanization patterns of hamadryas baboons and to see whether they support the hypothesis that this species is especially dependent on the morning sun. Our work also underscores the importance of searching Eritrea and neighboring countries for corroborating archaeological evidence, such as Egyptian products, that could speak to Punt's location.

One wonders what the Puntite traders thought of the Egyptians' obsession with baboons. It is tempting to speculate that they were only too eager to exchange a local pest for Egyptian trade goods. But we have that cultural idiosyncrasy to thank for illuminating one of the most important trade routes in human history. SA

FROM OUR ARCHIVES

The Pyramid Effect. Zach Zorich; November 2015.

scientificamerican.com/magazine/sa

Zooonar GmbH *Alamy*

PAPIO HAMADRYAS **was the only baboon species deified by ancient Egyptians.**

ASSEMBLED AND READY
The fully built James Webb Space Telescope (JWST) awaits its December launch at a Redondo Beach, Calif., facility run by its prime contractor, Northrop Grumman.

ASTRONOMY

First Light

The long-delayed successor to the Hubble Space Telescope is finally ready to launch

By Clara Moskowitz | Photographs by Chris Gunn

Clara Moskowitz is a senior editor at *Scientific American*, where she covers space and physics.

Chris Gunn is a Washington, D.C.–based photographer who specializes in science and technology. He is NASA's lead photographer for the James Webb Space Telescope project.

AS A NASA PHOTOGRAPHER, Chris Gunn has been documenting the James Webb Space Telescope (JWST) from its early days. Since 2009 he has captured every milestone and witnessed nearly all the pieces of the spacecraft being put together and tested. The telescope is scheduled to reach space in December, and in the months that follow it will open its 6.5-meter-diameter eye on the sky. At this point, the subject of Gunn's photography will become a photographer itself. "Seeing those first-light images is what's most important to me," Gunn says.

A joint project of NASA, the European Space Agency and the Canadian Space Agency, JWST will observe some of the oldest galaxies in the universe, image new planets and solar systems forming around other stars, and even probe the planets of our own system in new detail. The most ambitious and expensive telescope ever built, the $10-billion Webb is optimized to observe infrared light, the better to study objects from the distant and ancient universe. "We've been waiting for an observatory like this for a while," says Knicole Colon, deputy project scientist for exoplanet science for JWST. "Webb will see back to the very earliest galaxies, as far back in time as we can, and the sensitivity of the telescope will let us see deeper into exoplanet atmospheres than we've ever seen."

To avoid contaminating heat from the sun and Earth, Webb will fly to a vantage point 1.5 million kilometers from our planet, where it will unfurl a sun shield the size of a tennis court for additional protection. This delicate maneuver, as well as the deployment of its primary and secondary mirrors, must go perfectly—sending astronauts to repair the telescope, as happened with Hubble, is not an option. "I am extremely confident that our engineers have really done a great job of testing everything they can possibly test," says Heidi Hammel, an interdisciplinary scientist for JWST. "At some point you just have to fish or cut bait. We're ready to go."

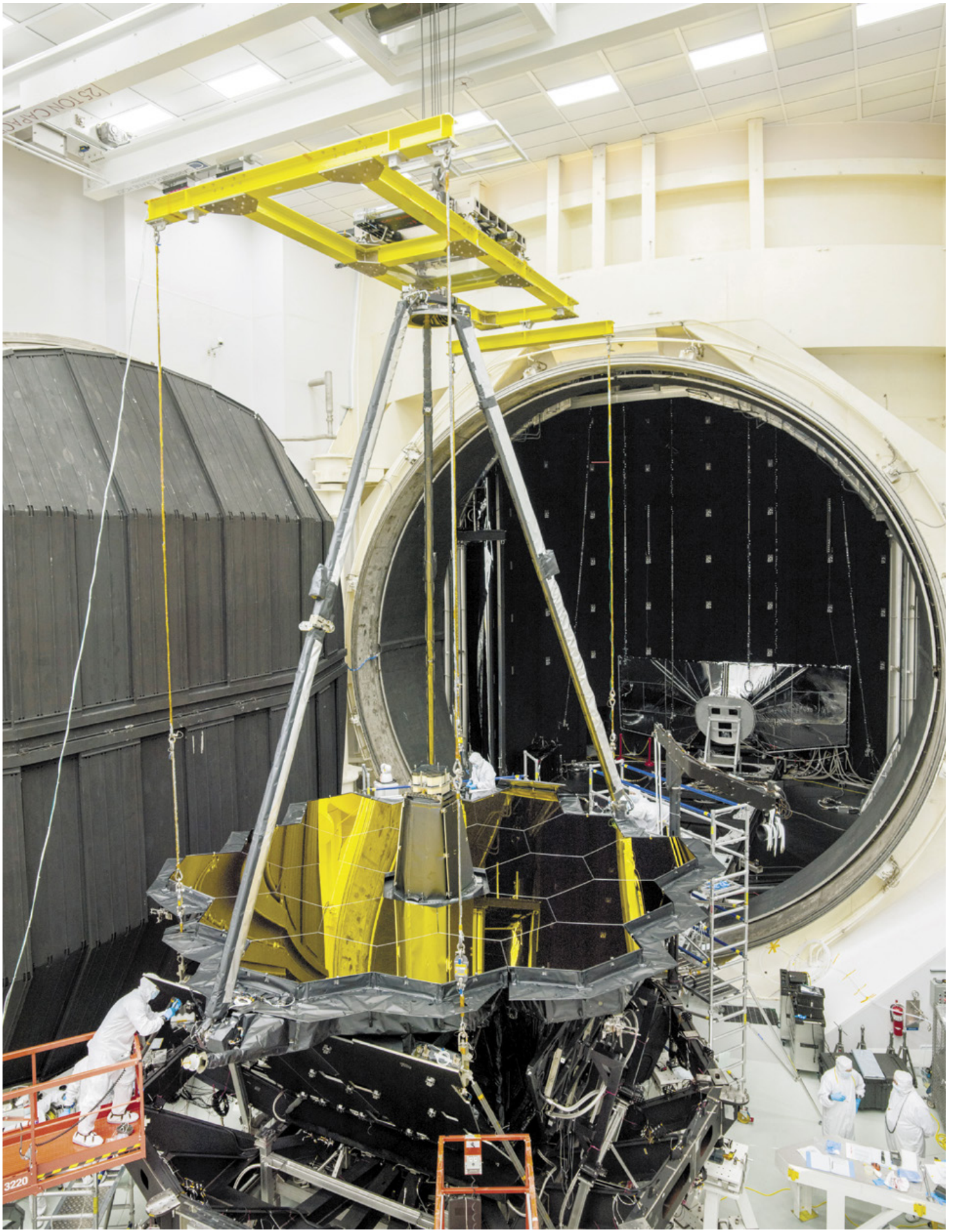
JWST's road to launch has been rocky. Early on the observatory was supposed to cost no more than $1 billion and lift off around 2007, but it was plagued by management problems, technical challenges, budget overruns and schedule delays. When the spacecraft finally launches on an Ariane 5 rocket from French Guiana, the thousands of scientists, engineers and others who have toiled on it will be hoping for a smooth ride. "For me, this is a huge, huge chunk of my life," Gunn says. "It's almost akin to raising my child but obviously a little bit different because there have been so many other parents."

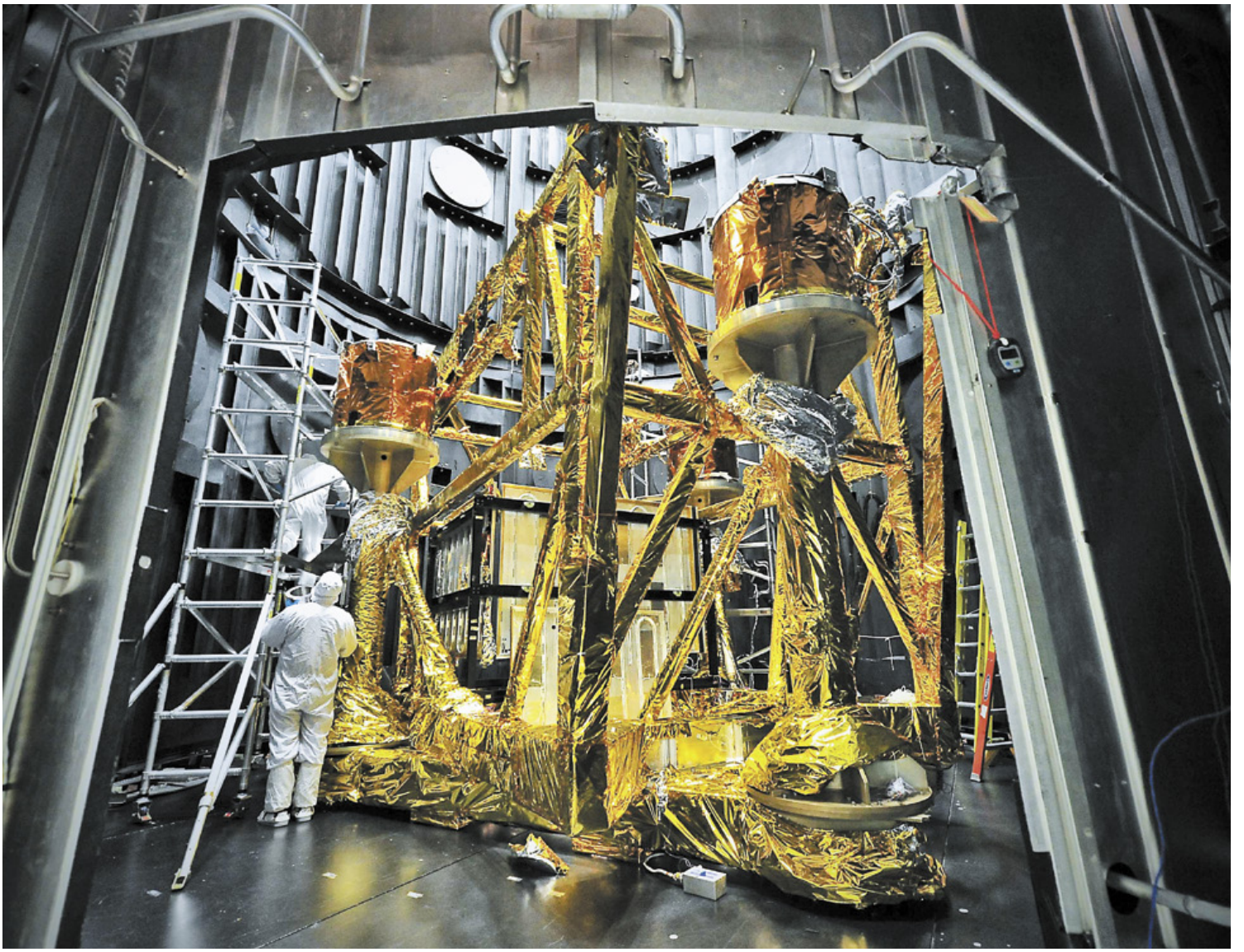
MIRROR ARRIVAL

Technicians inspect one of the 18 hexagonal mirror segments that will form Webb's primary mirror. The beryllium pieces, each coated with 0.12 ounce of gold, were designed to be exceptionally strong yet light at just 20 kilograms each. They are mounted to a foldable structure that will be packed tight into the rocket for liftoff and then open in space. "This [moment] was extremely memorable because most of the people in the photograph had never seen the mirrors before in person," Gunn recalls. "The mirrors came in initially one by one, then two and three at a time. Each inspection lasted for an hour or an hour and a half."

FRAGILE LOAD
Workers transport one of the observatory's mirror segments, which arrived at Goddard in specially constructed shipping canisters from their manufacturer, Ball Aerospace in Colorado. Each individual mirror is 1.32 meters wide; collectively they produce an observing area six times larger than the Hubble Space Telescope's mirror.

SUPER-CLEAN ROOM
Before JWST's disparate parts all came together, its mirrors and instruments were carefully assembled in the High Bay Clean Room at NASA's Goddard Space Flight Center in Greenbelt, Md. The 1.3-million-cubic-foot room, one of the largest of its kind in the world, includes an entire wall of HEPA air filters to stop contaminants such as dirt and dust from reaching the telescope's sensitive optics.





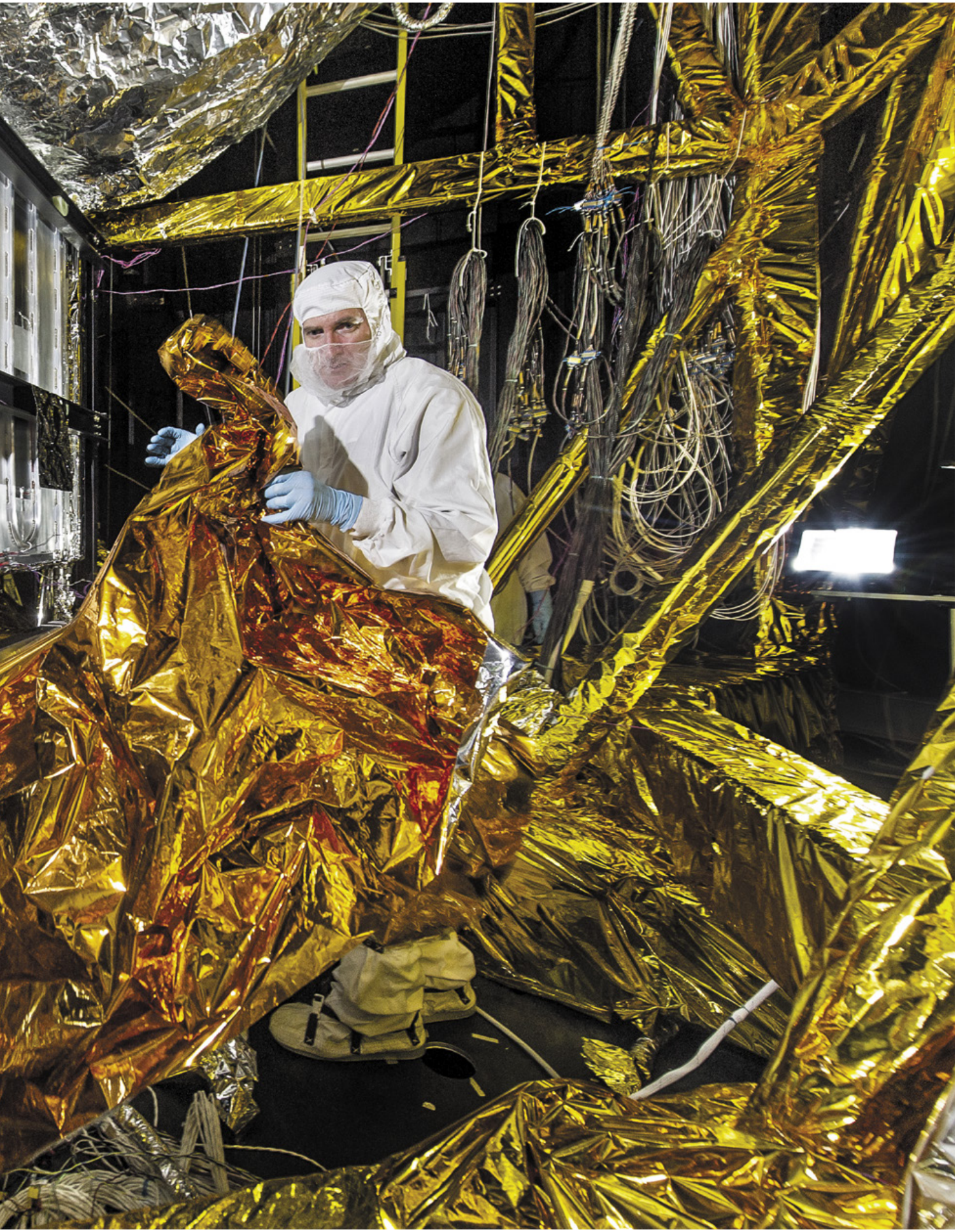
GOLDEN CAGE

Before the real flight hardware was built and tested, an ersatz version of JWST's optics called the Optical Telescope Element Simulator was subjected to spacelike conditions in the Space Environment Simulator at Goddard. There gold thermal blankets encase a system of supports and thermal-control devices, including a group of liquid-nitrogen panels that help to keep the simulator at around 100 kelvins, to match the temperature extremes it will experience beyond Earth.

COLD AND AIRLESS

To make sure JWST can withstand the frigid vacuum conditions of space, its instruments and optics underwent 100 days of cryogenic testing inside Chamber A, a massive thermal-vacuum testing room at NASA's Johnson Space Center in Houston. A 40-ton circular door, 12.2 meters wide, encloses the largest high-vacuum, cryogenic-optical test chamber in the world, which was used in the 1960s to assess hardware for the Apollo moon missions.

REPEATED SCRUTINY
A technician carefully handles the gold foil used to enshroud instruments during cryogenic testing in the Space Environment Simulator. This intensive, repeated testing is meant to ensure JWST will work once it reaches its destination, where scientists will have no recourse, short of software fixes, to intervene if something goes wrong. "It's definitely a complicated observatory, and it's something that we cannot service, like we can service Hubble," Colon says. "But Webb has a lot of redundancies in its mechanical systems, and people have been very careful in testing every little aspect of it."



EXTRA BLANKETS

Webb's elaborate sunshield is not the only thing that will help keep the telescope cold. A protective layer of blanketing behind the primary mirror, called a frill, will block unwanted light and heat from reaching the infrared sensors. Because the observatory is open—it lacks the usual cylindrical canister surrounding its optics that most telescopes have—this extra layer will help filter out even faint contamination from stars and galaxies behind the mirror.

LIGHTS OUT

Technicians examine JWST's mirrors during a "lights-out" test. "It's an evening shot because they had to do this test in the dark," Gunn says. "I've always wanted my images to speak to the amount of work that's actually going into the project. When people talk about Webb and how much time it's taken to build, I think if they had an appreciation for all the work that's gone into it, the time wouldn't factor in the way it does."

FROM OUR ARCHIVES

Origami Observatory. Robert Irion; October 2010.

scientificamerican.com/magazine/sa

Innovations IN

SPECIAL REPORT FROM
SCIENTIFIC AMERICAN
nature

Gene Therapy

PRODUCED WITH SUPPORT FROM PFIZER

Gene Therapy Comes of Age

GENE THERAPY HAS COME A LONG WAY SINCE its first human proof-of-concept trials in the 1990s. The approach—which involves fixing or replacing a disease-causing gene or changing its activity—has recorded some remarkable successes and some devastating missteps. In the past decade those extreme ups and downs have leveled off, and now gene therapy, in a variety of forms, has begun advancing at a rapid pace. This special report explores how the field has moved beyond its early failures and grown to encompass an ever expanding vision of what genomic medicine is and what it can accomplish.

Over the past few years not only has the discipline changed but the very definition of gene therapy has evolved. Today the field includes not just direct, permanent changes to a cell's DNA but also transient changes to how genes are translated into proteins. Researchers have now reported a number of success stories: they have alleviated some cases of blindness, cured cancers, addressed the underlying cause of sickle cell disease, and begun to treat congenital disorders, such as spinal muscular atrophy, that might otherwise be lethal.

The history of gene therapy has had a lot to overcome, both in reputation and at the lab bench. Early tragedies led to a scientific reckoning of sorts—while many researchers turned away from the field entirely, others began to pursue ways to prevent some of the most serious side effects. What has resulted is a range of new viral vectors, engineered to incorporate their genetic cargo more safely and efficiently into the genome, as well as the rapid adoption and development of other tools, such as the Nobel Prize–winning technique known as CRISPR.

Gene therapy has more than compensated for its shaky start, and the field managed to rehabilitate not only its science but its reputation. Many now associate the approach with the potential for seemingly miraculous cures, an association that can be as harmful as it can be helpful. For both patients and the public, the potential for such treatments evokes not fear so much as an abundance of hope. And with that hope comes other problems: problems of overexpectation, of affordability and of accessibility. Current gene therapy approaches are pricey and not easily available, both issues that limit their possible reach. Solving these problems may be the field's next big challenge.

Lauren Gravitz, Contributing Editor

INSIDE

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Cover and main illustrations by Luisa Jung

The Gene Fix

Various gene therapy approaches are already approved for treating blood cancers and a few rare disorders. In the not so distant future, they may become standard care

By Esther Landhuis

THREE DECADES AFTER ITS FIRST, faltering steps in humans, gene therapy is emerging as a treatment option for a small but growing number of diseases. Although the concept faced scientific and ethical uncertainty when it was floated in the 1970s, the foundation of the approach—replacing or fixing a single, disease-causing gene—has proved solid. Researchers have developed different ways to correct or influence the way someone's genes function and used those techniques to create therapies for several blood disorders, as well as degenerative eye and muscle diseases. More than half a dozen such treatments have gained approval in the U.S. in the past five years, and numerous others, aimed at a variety of conditions, are progressing toward clinical trials.

Existing gene therapies rely on two fundamental approaches. The more common approach draws blood from the patient and reprograms specific cells within the laboratory before reinjecting them into the person's body. The other method delivers gene treatments directly into the body, usually to easier-to-reach areas such as the eye. Now the field is beginning to mature and move beyond these initial tactics. Continued advances have made gene delivery safer and more effective, leading to dozens of human trials in new tissues, such as the liver and heart. Other approaches are pushing beyond the original definition of gene therapy, with cutting-edge molecular tools that fix errors within genes rather than replacing or inserting a whole gene.

Yet despite recent progress, gene therapy faces numerous hurdles on the path to wider clinical use—chief among them is how to target specific tissues without triggering an immune response. Broader, long-term challenges include improving both manufacturing efficiency and cost: Gene therapy treatments in the U.S. currently average more than $400,000 per dose. Nevertheless, with so much potential and so many patients in need of new solutions, gene therapy will only continue to grow in both prominence and potency.

EARLY SUCCESS AND SHOCK WAVES

THE CONCEPT UNDERLYING the original gene therapy approaches, some of which are still in use, is fairly straightforward: When a disease results from a missing or dysfunctional gene, deliver a functional copy of the gene into affected cells. That, says Prashant Mali, a bioengineer at the University of California, San Diego, was the "version 1.0 definition of gene therapy."

One of the first attempts came in 1990, when researchers at the National Institutes of Health treated two young girls with severe immunodeficiency caused by a missing enzyme. In that trial, as with many current treatments, the therapeutic genes needed to produce the enzyme hitched a ride into the target cells inside engineered viruses, which had large chunks of their genome stripped out. This rendered the virus unable to replicate while making space for the delivery of the needed human genes. In essence, says Charles Gersbach, director of the Center for Advanced Genomic Technologies at Duke University, the approach capitalized on the virus's ability to infect human cells while "taking advantage of the viral shell as a Trojan horse to deliver therapeutic gene cargo."

The NIH team drew some of the girls' blood to isolate white blood cells, which were then "infected" with the viruses that carried the gene encoding the missing enzyme. Next the team infused the corrected cells into the girls. Each child received about a dozen more infusions over the next 18 to 24 months. The treatment wasn't a cure, but it lessened their symptoms and proved the approach could be used safely. That, in and of itself, was "a major milestone," Gersbach says.

A flurry of new gene therapy trials quickly followed, but in 1999 18-year-old Jesse Gelsinger died when an experimental gene treatment designed to treat his metabolic liver disease sent his immune system into overdrive. A few years later, in 2003, researchers reported that several people treated for immunodeficiency developed leukemias, an unfortunate result of the virus randomly inserting its cargo into cancer-promoting regions of the genome.

Researchers began to think, "'Wait a minute, maybe we don't understand this as well as we thought we did,'" Gersbach says. Gene therapy stalled for the better part of a decade. Clinical trials on hold, researchers turned all their attention back to the lab—studying and tweaking viral vectors, removing additional genes, and treating them with chemicals to make them safer and more effective at reaching target cells.

The renewed focus provided time and space for a better understanding of what worked and what didn't. Today, because of that progress, many gene therapies employ adeno-associated virus (AAV) or retrovirus vectors, each with their own pros and cons, in addition to improved versions of the adenovirus vector from the earliest trials. The genetic cargo delivered by most AAV vectors remains within the cell as separate, free-floating elements rather than stably integrating into the host cell's genome. That makes the vectors far less likely than earlier vectors to induce can-

cer but can make a treatment less durable, depending on how long the therapeutic genes remain in the host cell. On the other hand, because they are small, they can infect a broad range of cells and spread efficiently within tissues. Retroviruses offer different advantages. They can hold larger and more complex genes than AAV vectors. And some, such as lentiviruses, tend to insert themselves into coding regions, the parts of the genome that get translated into proteins. This minimizes cancer risk while conferring longer-lasting benefits than AAV vectors.

A FIELD REAWAKENS

GENE THERAPY GOT A FRESH START in the early 2010s, when researchers in Pennsylvania and Maryland independently reported results from trials for the treatment of leukemia or lymphoma. The experimental therapies trained and turbocharged the patients' immune systems so they could detect and destroy cancer cells. To do this, the scientists had to engineer genes that would equip cells to recognize and kill tumors. They put those genes into retroviral vectors and delivered them to T cells, immune cells that had been isolated from the subjects' blood. When the treated T cells were reinfused, they put the cancer into remission. "Everything was looking really promising again," says Cynthia Dunbar, a physician-scientist who studies blood cell treatments at the National Heart, Lung, and Blood Institute.

The U.S. Food and Drug Administration has since approved several of these T cell treatments, known as chimeric antigen receptor (CAR) T cell therapies, for certain lymphomas and leukemias, as well as multiple myeloma. Because CAR T cell treatments don't address gene dysfunction per se but rather endow T cells with tumor-hunting capabilities, some have debated whether they qualify as gene therapies at all. Methodologically, though, CAR T boosts cell function by using viral vectors to deliver genes—similar to the earliest forays. "What you define as 'gene therapy' is a little bit gray on the edges," Dunbar says.

Another genetic approach that is a bit gray around the categorical edges is known as oligonucleotide therapy. Rather than correcting existing genes, this technique uses short sequences of nucleic acids, or oligonucleotides, to influence how cells translate genes into proteins. One such treatment, nusinersen (Spinraza), binds to intermediary RNA molecules to trick cells into making more of a protein that is missing in people with spinal muscular atrophy.

GENE THERAPY 2.0

IN THE PAST DECADE technological advances have ushered in a new era, and the definition of gene therapy continues to evolve, Mali says. The newest approaches forgo the delivery of healthy genes and instead aim to precisely repair the gene within the cell. When there is a mutation or other error in the genome, Mali says, now the question is, "Could we actually go in and fix it?"

This innovation is fueled by the Nobel Prize–winning discovery of CRISPR-Cas9, an immune defense system in bacteria that detects specific DNA sequences of invading viruses and directs an enzyme to slice up and destroy the viral genome. The system has utility far beyond bacteria: Scientists found they could also use it to make precise cuts within the mammalian genome. In just seven years the technique has moved from in vitro lab experiments in mammalian cells to human trials.

The "cargo" in CRISPR-based therapies is not a piece of DNA but the gene-editing system itself, introduced into cells either by a virus, within a nanoparticle, or on its own as an RNA-protein complex. The therapies can be used ex vivo (outside the body) to alter cells in the lab before returning them to the patient or by sending gene-editing tools directly to affected tissues, where they edit cellular genomes.

Several dozen companies are now developing such CRISPR-based therapies. One early-phase clinical trial employed an ex vivo gene-editing method to treat people with sickle cell disease or with a related blood disorder called beta thalassemia. Those researchers reported results for their first two subjects in January 2021. And in June another company reported the first-ever successful trial of direct gene editing, which used nanoparticles to deliver CRISPR-Cas9 components into liver cells and inactivate a gene implicated in a rare disease called transthyretin amyloidosis.

The newest approaches forgo the delivery of healthy genes and instead aim to precisely repair the gene within the cell.

Emerging methods have allowed for greater precision and nuance—exchanging individual nucleotides, for example, or temporarily dampening a gene's activity without changing its DNA—giving researchers the latitude to set their sights ever higher. They are working on treatments for neurological diseases, autoimmune disorders and additional cancers. Over the long term they aim to move beyond single-gene disorders to treat conditions caused by interactions of multiple genes, such as cardiovascular disease and chronic pain. With gene treatments successfully alleviating some illnesses, researchers, clinicians and patients are hoping to sustain the progress of the past decade and establish gene therapy as a cornerstone of modern medicine.

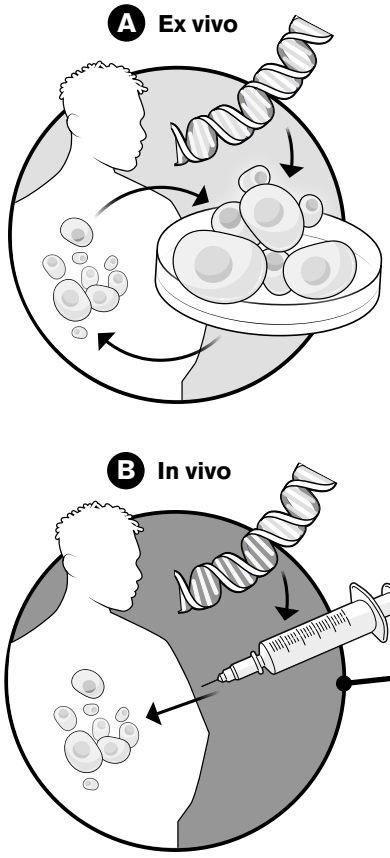
Esther Landhuis is a freelance science and health journalist based in the San Francisco Bay Area. Her stories about life science technologies have also appeared in *Nature* magazine.

Editing the Book of Life

Since the concept of treating diseases by targeting their underlying genes arose half a century ago, gene therapy research has advanced dramatically. Recently the pace of progress has intensified. In the past five years the U.S. Food and Drug Administration has approved more than half a dozen gene therapy products aimed at several types of cancer and inherited conditions. These treatments work in various ways, such as delivering healthy genes to affected cells or reshaping the activity of existing genes. Some of the newest approaches, which have shown promise in early-stage clinical trials, aim to fix errors in the genome itself. And experts expect the pace of new product approvals will continue to pick up. *—E.L.*

Location

Ex vivo gene therapy involves removing blood, bone marrow or other tissues from a patient, isolating the cells of interest and correcting them in the lab before reinfusing them back into the body **A**. In vivo approaches send therapeutic genes, gene modulators or gene-editing tools directly to cells in affected tissues within the patient's body **B**.

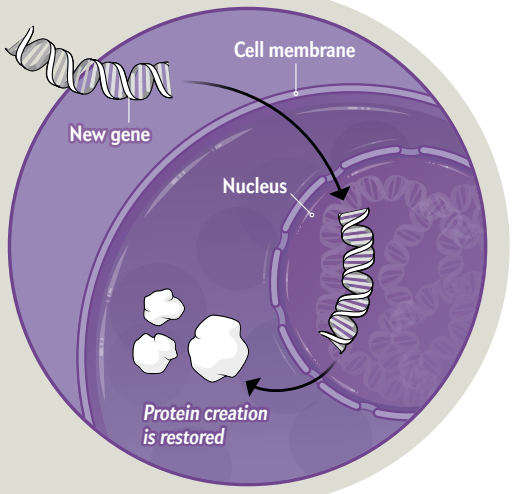


Technique

Gene therapies use various strategies to supply cells with healthy genes, influence gene activity or tweak the genome directly. Each of these methods has advantages and drawbacks, including treatment duration and potential side effects.

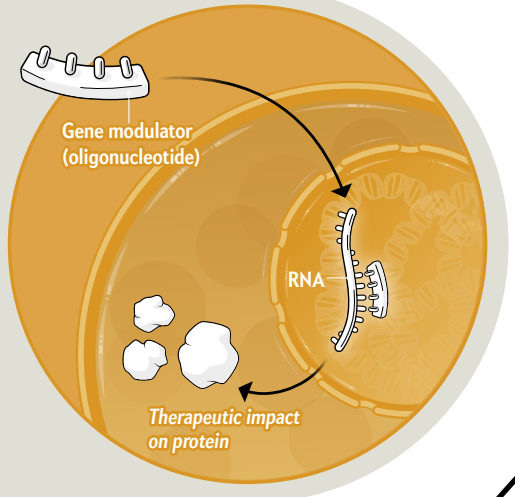
Introduce a New Gene

This approach, the first to be tested in humans, equips affected cells with a working copy of the gene that is missing or malfunctioning in the disease. Whereas this strategy can work for diseases traced to a single genetic glitch, many conditions involve multiple genetic and environmental factors.



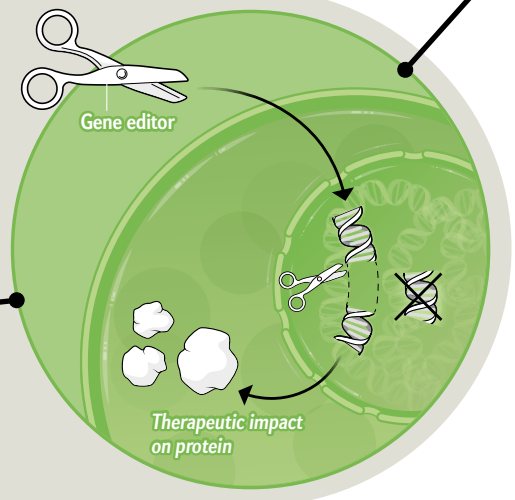
Modulate an Existing Gene's Activity

Other therapies send short sequences of nucleic acids, called oligonucleotides, into affected tissues where they can influence how cells build working proteins from underlying genetic code. Unlike gene replacement or correction, this approach is not permanent, and patients must receive regular infusions for continued benefits.



Edit Gene Directly

These approaches aim to fix errors in specific genes of affected cells. Newer methods use a gene-editing system called CRISPR-Cas9 to make precise changes in the genome.

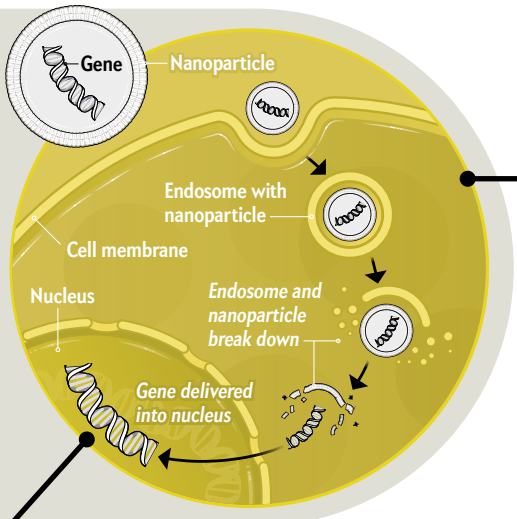


Cargo Delivery Method

Decades of research have honed several methods for carrying either genes, or tools to edit those genes, into target cells. Not only do they have to reach the cell, but they must also evade the immune responses that are often triggered when foreign substances enter the bloodstream.

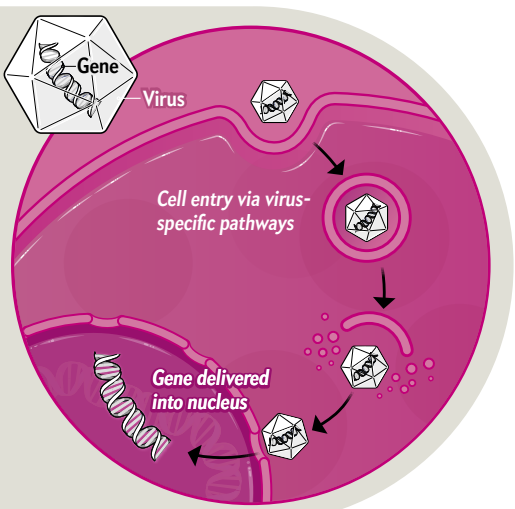
Nanoparticles

These gene therapies use nanoparticles to carry genes or gene-editing tools directly into cells of affected tissues. Nanoparticles can be chemically modified to avoid immune detection and to better target cells.



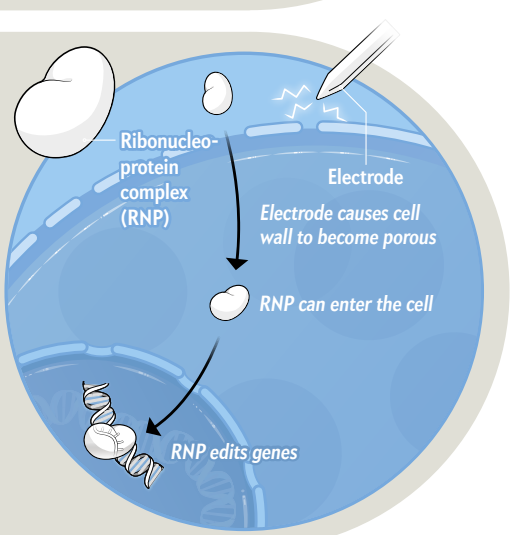
Virus

This approach delivers genes or gene-editing cargo with viruses that researchers have engineered to minimize chances of harmful immune responses and unintended effects on healthy cells.



Other

Clinical trials are testing newer approaches that send gene-editing machinery into cells as complexes of molecules that work together to target and make precise cuts within specific DNA sequences to delete or fix genes.



Examples

In a small study, people with an inherited disease called transthyretin amyloidosis that causes misfolded proteins responded well to an experimental in vivo gene-editing treatment, NTLA-2001 (Intellia Therapeutics/Regeneron), that uses nanoparticles to carry CRISPR-Cas9 into liver cells to inactivate the gene culprit.

A protein called SMN is necessary for motor neuron function, and people with spinal muscular atrophy have a mutation that decreases its production. Spinraza (Ionis Pharmaceuticals/Biogen)—an in vivo gene modulator—coaxes cells into making more SMN protein by boosting its production from a different, unmutated gene.

Leber congenital amaurosis and retinitis pigmentosa are forms of severe vision loss caused by genetic mutations. In certain cases, vision can be restored with Luxturna (Spark Therapeutics), which uses a virus to deliver the healthy gene into retinal cells.

Kymriah (Novartis) is the first approved gene therapy to equip a patient's own immune cells to fight cancer. The approach, known as chimeric antigen receptor (CAR) T cell therapy, involves isolating a patient's T cells and using a virus to equip them with receptors that enable them to recognize and kill certain kinds of tumor cells.

An experimental, ex vivo gene-editing treatment, CTX001 (CRISPR Therapeutics/Vertex Pharmaceuticals), boosted hemoglobin production in blood stem cells of trial participants with sickle cell disease or transfusion-dependent beta thalassemia.

Source: "The Once and Future Gene Therapy," by Karen Bulaklak and Charles Gersbach, in *Nature Communications*, Vol. 11; November 2020 (*reference*); Cynthia Dunbar *National Institutes of Health* (*expert reviewer*)

Graphic by Now Medical Studios

Overcoming Gene Therapy's Long Shadow

Serious side effects plagued the field's early years, but researchers are finding ways to minimize the risks

By Tanya Lewis

AUDREY WAS SIX MONTHS OLD when her parents first noticed something wasn't right. Without warning, her body stiffened, and her eyes rolled into the corners of their sockets for hours at a time. Despite visits to multiple specialists, no one knew what was wrong. Her doctors prescribed seizure medication—lots of it—which sedated her but did not stop the eye-rolling. Finally, they confessed that they did not know how to help and sent Audrey and her parents home with a handful of pamphlets about living with a disability.

Genetic tests later diagnosed Audrey with a condition known as aromatic L-amino acid decarboxylase (AADC) deficiency, caused by mutations in a single gene. The extremely rare disorder manifests in infancy and lowers the activity of AADC, an enzyme that is critical for making the brain-signaling chemicals dopamine and serotonin. It causes severe developmental and motor disabilities, as well as sleep and mood problems. Most children with the condition are unable to talk, sit up or support their own weight.

After years of frustration, Audrey's parents enrolled her in a clinical trial led by Krystof Bankiewicz, a professor of neurosurgery at the University of California, San Francisco, and the Ohio State University College of Medicine. The gene therapy Bankiewicz and his colleagues were testing uses a harmless virus as a vector to introduce an intact version of the gene responsible for making the AADC enzyme. Seven children participated in the trial. The researchers injected the virus directly into each child's brain near neurons they hoped would start making AADC and, subsequently, dopamine.

The children ranged in age from four through nine years old at the beginning of the trial (Audrey was six at the time). The results were dramatic: by three months after surgery, six of the seven children stopped having oculogyric crises—the distinctive eye-rolling that is a hallmark of the disease. The seventh child also improved initially but died seven months later from complications of the disease itself, Bankiewicz says. A year postsurgery all six surviving children could control their heads normally, and four could sit independently. After a year and a half, Audrey and one other child were walking with hand support and learning to use muscles they had previously been unable to command. So far none of the children has shown any serious side effects.

Outcomes like Audrey's would not have been possible without decades of research and patients who volunteered for experimental treatments, knowing they could be risking their lives, to help move gene therapy forward. Serious side effects, some deadly, threatened to derail the field in its early years, prompting researchers to step back and reconsider their approach. Convinced of the promise of genetic cures and of the potential to find safer, more precise gene delivery methods, they persisted.

Since then, gene therapy has yielded some notable successes [see "Success Stories," on page S12]. Yet the quest to control side effects is far from over. As in any pioneering field of medical science, researchers must strike a balance between advancing knowledge that could help cure devastating diseases and proceeding with caution to protect patients.

FIRST DO NO HARM

JESSE GELSINGER WAS 18 years old in 1999, when he joined one of the first clinical trials of gene therapy [see "The Gene Fix," on page S3]. Gelsinger suffered from an inherited genetic disorder called ornithine transcarbamylase (OTC) deficiency, which causes toxic levels of ammonia to build up in the blood. Untreated, that buildup can lead to vomiting, lethargy and, in severe cases, death. The condition affects up to one in 50,000 infants and is caused by mutations in the *OTC* gene. Standard treatment for the condition involves a restricted diet and supplementation known as alternative pathway therapy. Gelsinger was being treated for the condition and had a mild case, but he occasionally experienced episodes of high ammonia levels, known as hyperammonemia, once even slipping into a coma.

The gene therapy trial he enrolled in used a type of cold virus known as an adenovirus that had been engineered to deliver a working version of the *OTC* gene to his liv-

er cells. Gelsinger was one of two participants receiving the highest dose. Within days of the treatment, however, his condition declined rapidly. His body launched a severe inflammatory response that led to organ failure and, ultimately, brain death.

A few years later several children who had been treated with gene therapy for a severe immune disease developed cancer.

Research funding dried up, and many investigators abandoned the field. But those who remained began to make improvements in both the safety and the efficacy of viral vectors. They also began exploring a gene-editing method called CRISPR, which could enable more targeted therapies but came with a new set of risks.

Gene therapy has come a long way since Gelsinger died—Audrey is living proof of that. Yet researchers remain vigilant about the specter of side effects. "We're in a very different place now," says Mark Batshaw, the physician who helped to lead the trial involving Gelsinger more than 20 years ago. "We know a lot more about vectors. We know a lot more about the immunity that is associated with that. And I think there's a lot more care."

After Gelsinger's death, the U.S. Food and Drug Administration banned James Wilson, the scientist whose laboratory developed the therapy Gelsinger received, and his institution, the University of Pennsylvania's Institute for Human Gene Therapy, from conducting human trials for at least five years. An FDA notice cited repeated and deliberate violations of the trial protocol for an investigational drug. The agency suspended all research at Wilson's institute, too.

But it was not the end for gene therapy or for Wilson's career. "There was a precipitous decline in enthusiasm in supporting the field," Wilson says. Nevertheless, "there were a few of us who continued to work on gene therapy," he says. "We pivoted from clinical applications to basic science around the delivery of genes." Wilson and his colleagues turned back to the lab bench to understand what went wrong in Gelsinger's death. Their best hypothesis is that he had antibodies to adenovirus from a previous exposure to the virus and that these relics of a former infection supercharged his immune system's response to the adenovirus vector.

Wilson and other researchers took a hard look at the issue of side effects and how to minimize them. Because the viral vector seemed to be the biggest risk, they switched to adeno-associated viruses (AAVs), which proved far safer. Today AAVs are used in numerous therapies, including an approved drug for spinal muscular atrophy. "I'm glad we stayed with it," Wilson says.

LEARNING FROM FAILURE

AROUND THE SAME TIME as the Gelsinger trial, scientists in France and England were working on a therapy for severe combined immunodeficiency syndrome (SCID), a genetic condition that affects at least one in 50,000 babies. It is sometimes referred to as "bubble boy disease" because those afflicted with it, primarily boys, are born without an immune system and must live in isolated, sterile environments to keep from getting sick. It can be cured with a bone marrow transplant from a matched donor, but only about a quarter of affected children find such a match. Without treatment, children with SCID usually die within the first year of life.

For their vector, the researchers turned to a group of viruses called gammaretroviruses because they believed them to be efficient at delivering genetic material to cells. In a pair of clinical trials, they targeted a form of SCID that is passed down from a mother to her baby on an X chromosome, known as SCID-X1. It is caused by errors in a gene that encodes a protein called IL2RG. In both trials, the patients' own bone marrow stem cells were collected and isolated. The researchers used a gammaretroviral vector to insert a working copy of the *IL2RG* gene into them, then reinfused the modified cells. Initially the therapy appeared somewhat successful: most of the 10 children who were treated started producing functional T cells—an important component of a working immune system. But within three to six years half the subjects developed leukemia, and one died. The viral vectors are believed to have activated a known cancer-causing gene. The FDA halted all U.S. trials involving a retroviral vector aimed at modifying bone marrow stem cells.

"Our knowledge came from animal models," says Marina Cavazzana, a pediatrician and hematologist at Paris Descartes University's Necker Hospital, who wrote the clinical protocol and handled patient follow-up for the clinical trial in France. The problem, she says, is that the animal models were unable to predict human toxicity. "I stopped the clinical trial, we came back to the bench, and we tried to explain the reason for these side effects. And we came back again to the clinic," she says.

David Williams, chief of hematology and oncology at Boston Children's Hospital, was involved in those early SCID trials. "In the end," he says of both the SCID trials and Gelsinger's trial, "you have to try these things in human beings to completely understand the benefits versus the risks."

When Williams and his colleagues resumed their work on SCID a decade later, they created a modified version of their gammaretrovirus to avoid activating cancer-causing oncogenes. It still prompted the development of just one type of immune cell, however, and recipients required continued intravenous injections to maintain production. But nearly a decade later none of the subjects has shown signs of leukemia or other side effects.

It was yet another viral vector that helped to push the SCID effort across the finish line. In 2016 a team led by Ewelina Mamcarz, a bone marrow transplant specialist at St. Jude Children's Research Hospital in Memphis, launched a trial for SCID-X1 using a lentivirus (a virus related to HIV) as a vector. Researchers built a "firewall" into it that would prevent the activation of any parts of the genome that might cause leukemia. Mamcarz and her colleagues also pretreated patients with chemotherapy to make room for the modified bone marrow stem cells.

Mamcarz's team has treated a total of 18 infants with this gene therapy. To date, about five years post-treatment, none has developed leukemia. "We are hopeful we're kind of out of the woods now, but we will continue to monitor patients closely," Mamcarz says. "My anxiety level was much higher when we started [the trial] because there was so much unknown," she says. "I think I can sleep at peace now, years into this gene therapy in infants, but we never rest."

Concerns about gene therapy's side effects have also been front of mind for researchers working on other conditions. Sickle cell disease, which affects about 300,000 infants born every year and occurs more commonly among people of African descent, has long been a prime tar-

Photograph by Timothy Archibald

Audrey, with her mother, Carrie, three years after her successful gene therapy.

get for gene therapy because it, too, is caused by a single-gene defect. This condition causes red blood cells to take on a sickle shape and clump together, making them unable to transport oxygen efficiently. People with the disease experience debilitating pain crises, strokes and other problems, and it can be fatal. Although treatments exist, the only cure is a risky bone marrow or stem cell transplant.

Bluebird Bio, a biotech company in Cambridge, Mass., reported promising results from a clinical trial of its sickle cell gene therapy in late 2020. Nineteen patients were treated with a lentiviral vector containing a working version of the gene that encodes a component of adult hemoglobin—all 19 stopped having severe pain crises within six months. But more than five years later two patients in a different cohort developed a rare blood cancer called acute myeloid leukemia.

The FDA placed a clinical hold on the Bluebird Bio study, as well as several similar trials, while the company investigated these cases. Bluebird Bio's own investigation found that the leukemia was unlikely to be related to gene therapy. According to Rich Colvin, Bluebird Bio's chief medical officer, in one of the cases the viral vector was not found in the cancer cells, and in the other, viral DNA was present but had not integrated into any gene known to be involved in leukemia development. In June 2021 the FDA lifted its hold on the trials, which have since resumed.

Bluebird Bio is also testing a gene therapy for patients with X-linked adrenoleukodystrophy (ALD), a devastating disease that primarily affects boys and gives them only a five- to 10-year life expectancy. In that trial, one of the 67 patients developed myelodysplastic syndrome, a condition that can lead to leukemia, and this time it was found to be related to the viral vector. The FDA has now placed the trial on hold. Colvin says the benefits of the therapy still outweigh the risk of ALD, which would have proved fatal. But he knows it is a delicate balance: "I think you have to have humility when you're manipulating the human genome."

RISK VS. BENEFIT

VIRAL VECTORS, by their very nature, can insert themselves into an undesired part of the target cell's genome. But newer technology is enabling much more precise edits to a gene. The CRISPR technique is already being used in some gene therapies. Although there is a potential risk of so-called off-target effects on other parts of the genome, these have not been observed in the early clinical trials.

In a trial sponsored by Cambridge, Mass.–based CRISPR Therapeutics and Boston-based Vertex Pharmaceuticals involving CRISPR gene therapy, two patients with sickle cell disease and 20 patients with a related condition called beta thalassemia saw near-complete improvement of their symptoms, according to unpublished data. Although longer-term follow-up is needed, David Altshuler, chief scientific officer at Vertex Pharmaceuticals, calls the results a "medical and scientific milestone."

With all new therapies, the risk of side effects must be considered in the context of the diseases being treated. A condition such as AADC deficiency can be fatal, and Audrey's mother, Carrie, knew that when she enrolled her daughter in the U.C.S.F. clinical trial. She was desperate and figured any improvement would be better than the status quo.

Three years after enrolling Audrey in the trial, Carrie says that her daughter is a "totally different kid." She doesn't have the eye-rolling anymore. She is learning to eat food by mouth and to speak some words. Thanks to her talking device—a touch-pad machine that allows her to activate spoken, computer-generated phrases—she can communicate. Carrie says that before the treatment, her daughter could understand what people were saying, but she could not express herself. "Now she can just really speak her mind," Carrie says.

Audrey continues to struggle with some things, including balance and speech. But her life today is far from what it might otherwise have looked like. And in that one gene therapy's success, Carrie says, other families can find hope. "If we don't do it, we know the end result," she says. But "if it can do anything, even a little bit, it's already a win."

Tanya Lewis is senior editor for health and medicine at *Scientific American*.

Success Stories

Gene therapy is beginning to fulfill its potential. Four therapies offer a glimpse of what's to come

By Jim Daley

After numerous setbacks at the turn of the century, gene therapy is treating diseases ranging from neuromuscular disorders to cancer to blindness. The success is often qualified, however. Some of these therapies have proved effective at alleviating disease but come with a high price tag and other accessibility issues: Even when people know that a protocol exists for their disease and even if they can afford it or have an insurance company that will cover the cost—which can range from $400,000 to $2 million—they may not be able to travel to the few academic centers that offer it. Other therapies alleviate symptoms but don't eliminate the underlying cause.

"Completely curing patients is obviously going to be a huge success, but it's not [yet] an achievable aim in a lot of situations," says Julie Crudele, a neurologist and gene therapy researcher at the University of Washington. Still, even limited advances pave the way for ongoing progress, she adds, pointing to research in her patients who have Duchenne muscular dystrophy: "In most of these clinical trials, we learn important things."

Thanks to that new knowledge and steadfast investigations, gene therapy researchers can now point to a growing list of successful gene therapies. Here are four of the most promising.

GENE SWAPS TO PREVENT VISION LOSS

Some babies are born with severe vision loss caused by retinal diseases that once led inevitably to total blindness. Today some of them can benefit from a gene therapy created by wife-and-husband team Jean Bennett and Albert Maguire,

who are now ophthalmologists at the University of Pennsylvania.

When the pair first began researching retinal disease in 1991, none of the genes now known to cause vision loss and blindness had been identified. In 1993 researchers identified one potential target gene, *RPE65.* Seven years later Bennett and Maguire tested a therapy targeting that gene in three dogs with severe vision loss—it restored vision for all three.

In humans, the inherited condition that best corresponds with the dogs' vision loss is Leber congenital amaurosis (LCA). LCA prevents the retina, a layer of light-sensitive cells at the back of the eye, from properly reacting or sending signals to the brain when a photon strikes it. The condition can cause uncontrolled shaking of the eye (nystagmus), prevents pupils from responding to light and typically results in total blindness by age 40. Researchers have linked the disease to mutations or deletions in any one of 27 genes associated with retinal development and function. Until gene therapy, there was no cure.

Mutations in *RPE65* are just one cause of inherited retinal dystrophy, but it was a cause that Bennett and Maguire could act on. The researchers used a harmless adeno-associated virus (AAV), which they programmed to find retinal cells and insert a healthy version of the gene, and injected it into a patient's eye directly underneath the retina. In 2017, after a series of clinical trials, the Food and Drug Administration approved voretigene neparvovec-rzyl (marketed as Luxturna) for the treatment of any heritable retinal dystrophy caused by the mutated *RPE65* gene, including LCA type 2 and retinitis pigmentosa, another congenital eye disease that affects photoreceptors in the retina. Luxturna was the first FDA-approved in vivo gene therapy, which is delivered to target cells inside the body (previously approved ex vivo therapies deliver the genetic material to target cells in samples collected from the body, which are then reinjected).

Spark Therapeutics, the company that makes Luxturna, estimates that about 6,000 people worldwide and between 1,000 and 2,000 in the U.S. may be eligible for its treatment—few enough that Luxturna was granted "orphan drug" status, a designation that the FDA uses to incentivize development of treatments for rare diseases. That wasn't enough to bring the cost down. The therapy is priced at about $425,000 per injection, or nearly $1 million for both eyes. Despite the cost, Maguire says, "I have not yet seen anybody in the U.S. who hasn't gotten access based on inability to pay."

Those treated show significant improvement: Patients who were once unable to see clearly had their vision restored, often very quickly. Some reported that, after the injections, they could see stars for the first time.

While it is unclear how long the effects will last, follow-up data published in 2017 showed that all 20 patients treated with Luxturna in a phase 3 trial had retained their improved vision three years later. Bennett says five-year follow-up with 29 patients, which is currently undergoing peer review, showed similarly successful results. "These people can now do things they never could have dreamed of doing, and they're more independent and enjoying life."

TRAINING THE IMMUNE SYSTEM TO FIGHT CANCER

Gene therapy has made inroads against cancer, too. An approach known as chimeric antigen receptor (CAR) T cell therapy works by programming a patient's immune cells to recognize and target cells with cancerous mutations. Steven Rosenberg, chief of surgery at the National Cancer Institute, helped to develop the therapy and published the first successful results in a 2010 study for the treatment of lymphoma.

"That patient had massive amounts of disease in his chest and his belly, and he underwent a complete regression," Rosenberg says—a regression that has now lasted 11 years and counting.

CAR T cell therapy takes advantage of white blood cells, called T cells, that serve as the first line of defense against pathogens. The approach uses a patient's own T cells, which are removed and genetically altered so they can build receptors specific to cancer cells. Once infused back into the patient, the modified T cells, which now have the ability to recognize and attack cancerous cells, reproduce and remain on alert for future encounters.

In 2016 researchers at the University of Pennsylvania reported results from a CAR T cell treatment, called tisagenlecleucel, for acute lymphoblastic leukemia (ALL), one of the most common childhood cancers. In patients with ALL, mutations in the DNA of bone marrow cells cause them to produce massive quantities of lymphoblasts, or undeveloped white blood cells, which accumulate in the bloodstream. The disease progresses rapidly: adults face a low likelihood of cure, and fewer than half survive more than five years after diagnosis.

When directed against ALL, CAR T cells are ruthlessly efficient—a single modified T cell can kill as many as 100,000 lymphoblasts. In the University of Pennsylvania study, 29 out of 52 ALL patients treated with tisagenlecleucel went into sustained remission. Based on that study's results, the FDA approved the therapy (produced by Novartis as Kymriah) for treating ALL, and the following year the agency approved it for use against diffuse large B cell lymphoma. The one-time procedure costs upward of $475,000.

CAR T cell therapy is not without risk. It can cause severe side effects, including cytokine release syndrome (CRS), a dangerous inflammatory response that ranges from mild flulike symptoms in less severe cases to multiorgan failure and even death. CRS isn't specific to CAR T therapy: Researchers first observed it in the 1990s as a side effect of antibody therapies used in organ transplants. Today, with a combination of newer drugs and vigilance, doctors better understand how far they can push treatment without triggering CRS. Rosenberg says that "we know how to deal with side effects as soon as they occur, and serious illness and death from cytokine release syndrome have dropped drastically from the earliest days."

Through 2020, the remission rate among ALL patients treated with Kymriah was about 85 percent. More than half had no relapses after a year. Novartis plans to track outcomes of all patients who received the therapy for 15 years to better understand how long it remains effective.

PRECISION EDITING FOR BLOOD DISORDERS

One new arrival to the gene therapy scene is being watched particularly closely: in vivo gene editing using a system called CRISPR, which has become one of the most promising gene therapies since Jennifer Doudna and Emmanuelle Charpentier discovered it in 2012—a feat for which they shared the 2020 Nobel Prize in Chemistry. The first results from a small clinical trial aimed at treating sickle cell disease and a closely related disorder, called beta thalassemia, were published this past June.

Sickle cell disease affects millions of people worldwide and causes the production of crescent-shaped red blood cells that are stickier and more rigid than healthy cells, which can lead to anemia and life-threatening health crises. Beta thalassemia, which affects millions more, occurs when a different mutation causes someone's body to produce less hemoglobin, the iron-rich protein that allows red blood cells to carry oxygen. Bone marrow transplants may offer a cure for those who can find matching donors, but otherwise treatments for both consist primarily of blood transfusions and medications to treat associated complications.

Both sickle cell disease and beta thalassemia are caused by heritable, single-gene mutations, making them good candidates for gene-editing therapy. The method, CRISPR-Cas9, uses DNA sequences from bacteria (clustered regularly interspaced short palindromic repeats, or CRISPR) and a CRISPR-associated enzyme (Cas for short) to edit the patient's genome. The CRISPR sequences are transcribed onto RNA that locates and identifies DNA sequences to blame for a particular condition. When packaged together with Cas9, transcribed RNA locates the target sequence, and Cas9 snips it out of the DNA, thereby repairing or deactivating the problematic gene.

At a conference this past June, Vertex Pharmaceuticals and CRISPR Therapeutics announced unpublished results from a clinical trial of beta thalassemia and sickle cell patients treated with CTX001, a CRISPR-Cas9-based therapy. In both cases, the therapy does not shut off a target gene but instead delivers a gene that boosts production of healthy fetal hemoglobin—a gene normally turned off shortly after birth. Fifteen people with beta thalassemia were treated with CTX001; after three months or more, all 15 showed rapidly improved hemoglobin levels and no longer required blood transfusions. Seven people with severe sickle cell disease received the same treatment, all of whom showed increased levels of hemoglobin and reported at least three months without severe pain. More than a year later those improvements persisted in five subjects with beta thalassemia and two with sickle cell. The trial is ongoing, and patients are still being enrolled. A Vertex spokesperson says it hopes to enroll 45 patients in all and file for U.S. approval as early as 2022.

DERAILING A POTENTIALLY LETHAL ILLNESS

Spinal muscular atrophy (SMA) is a neurodegenerative disease in which motor neurons—the nerves that control muscle movement and that connect the spinal cord to muscles and organs—degrade, malfunction and die. It is typically diagnosed in infants and toddlers. The underlying cause is a genetic mutation that inhibits production of a protein involved in building and maintaining those motor neurons.

The four types of SMA are ranked by severity and related to how much motor neuron protein a person's cells can still produce. In the most severe or type I cases, even the most basic functions, such as breathing, sitting and swallowing, prove extremely challenging. Infants diagnosed with type I SMA have historically had a 90 percent mortality rate by one year.

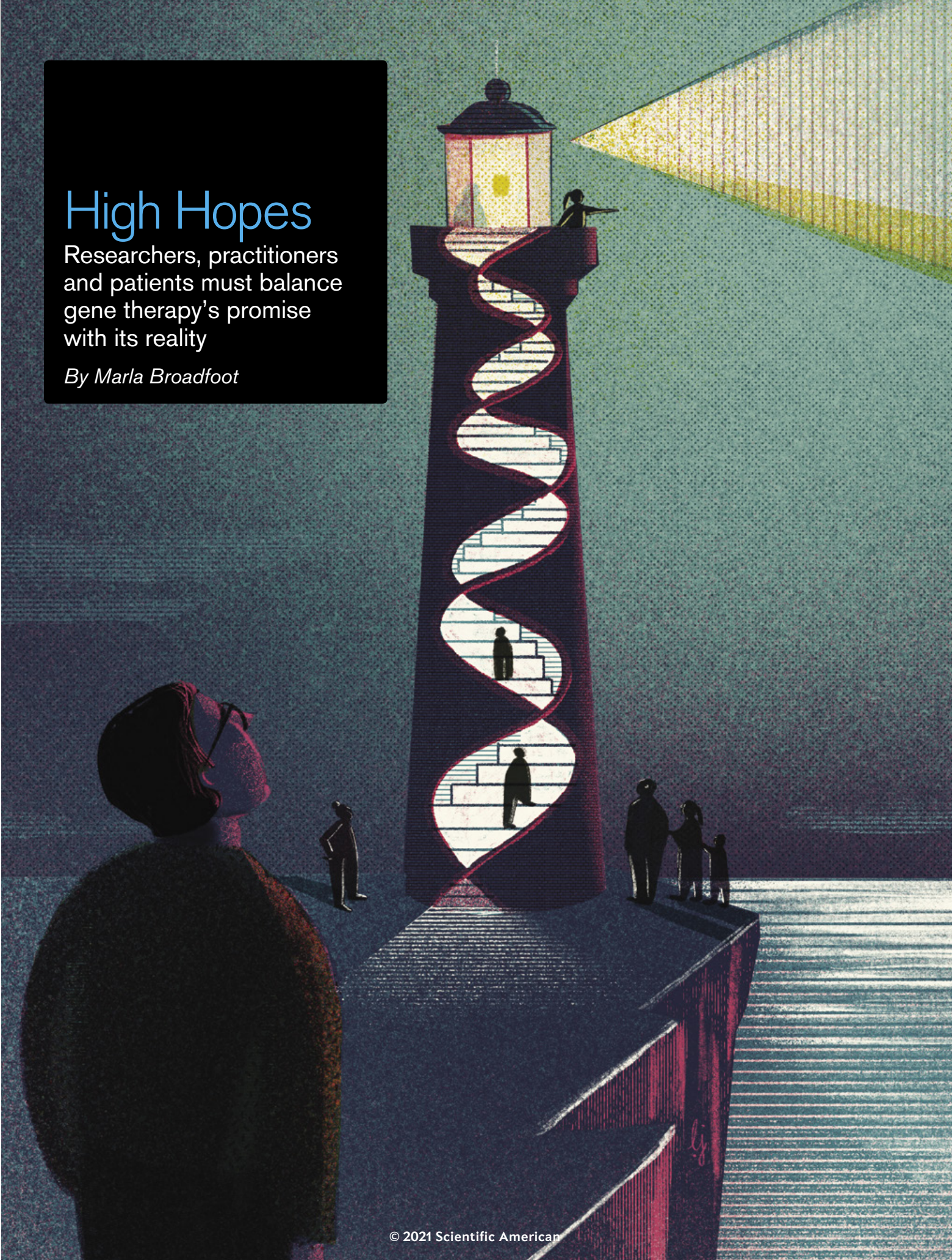
Adrian Krainer, a biochemist at Cold Spring Harbor Laboratory, first grew interested in SMA when he attended a National Institutes of Health workshop in 1999. At the time, Krainer was investigating how RNA mutations cause cancer and genetic diseases when they disrupt a process called splicing, and researchers suspected that a defect in the process might be at the root of SMA. When RNA is transcribed from the DNA template, it needs to be edited or "spliced" into messenger RNA (mRNA) before it can guide protein production. During that editing process, some sequences are cut out (introns), and those that remain (exons) are strung together.

Krainer realized that there were similarities between the defects associated with SMA and one of the mechanisms he had been studying—namely, a mistake that occurs when an important exon is inadvertently lost during RNA splicing. People with SMA were missing one of these crucial gene sequences, called *SMN1.*

"If we could figure out why this exon was being skipped and if we could find a solution for that, then presumably this could help all the [SMA] patients," Krainer says. The solution he and his colleagues hit on, antisense therapy, employs single strands of synthetic nucleotides to deliver genetic instructions directly to cells in the body [see "The Gene Fix," on page S3]. In SMA's case, the instructions induce a different motor neuron gene, *SMN2,* which normally produces small amounts of the missing motor neuron protein, to produce much more of it and effectively fill in for *SMN1.* The first clinical trial to test the approach began in 2010, and by 2016 the FDA approved nusinersen (marketed as Spinraza). Because the therapy does not incorporate itself into the genome, it must be administered every four months to maintain protein production. And it is staggeringly expensive: a single Spinraza treatment costs as much as $750,000 in the first year and $375,000 annually thereafter.

Since 2016, more than 10,000 people have been treated with it worldwide. Although Spinraza can't restore completely normal motor function (a single motor neuron gene just can't produce enough protein for that), it can help children with any of the four types of SMA live longer and more active lives. In many cases, Spinraza has improved patients' motor function, allowing even those with more severe cases to breathe, swallow and sit upright on their own. "The most striking results are in patients who are being treated very shortly after birth, when they have a genetic diagnosis through newborn screening," Krainer says. "Then, you can actually prevent the onset of the disease—for several years and hopefully forever."

Jim Daley is a freelance journalist from Chicago. He writes about science and health.



High Hopes

Researchers, practitioners and patients must balance gene therapy's promise with its reality

By Marla Broadfoot

MELISSA CREARY was three years old when she was diagnosed with sickle cell disease. The genetic condition, which affects more than 100,000 people in the U.S., is caused by a mutation that distorts red blood cells into sickle-shaped crescents that can get stuck in blood vessels and trigger episodes of agonizing pain. People in the thick of an episode have described the sensation as something akin to broken glass flowing through their veins. Others liken it to being electrocuted or stabbed.

Creary was in her early 40s when she developed a rare complication that turned her mild case into a severe one. Suddenly she began experiencing pain like never before. To dilute the sickle cells clogging her bloodstream, she had to undergo monthly blood transfusions. Creary felt tethered to the health-care system, literally and figuratively, in ways she had never expected.

"I remember moments where I was so angry all the time—angry at the betrayal of my body, angry at the betrayal of my genetics," says Creary, a health policy researcher at the University of Michigan. She recalls feeling resigned to the fate spelled out in her DNA. But as new gene therapies emerged, she began to see glimmers of hope.

Creary studies the biology, policy and social determinants of health related to sickle cell disease in the U.S. and Brazil. Her experience of severe sickle cell disease led her to talk with physicians about gene therapy in a new way—not as an academic exchanging ideas with colleagues but as a patient seeking answers. The dialogue progressed from talk of technology to deeper discussions about identity, history, trust, education, equity and emotion. Even now Creary is not sure what she would do if an experimental treatment were offered to her tomorrow.

A handful of gene-targeted treatments are under development for sickle cell disease, and hundreds more are being investigated for a variety of conditions, including cystic fibrosis, muscular dystrophy, hemophilia, Huntington's disease, HIV and cancer. Several gene therapies have already won FDA approval. The notion of rewriting a person's DNA is finally becoming a clinical reality.

In previous decades, conversations about gene therapy had to address and overcome the field's tragic past missteps. But today, after so much scientific progress, researchers and practitioners are dealing with an unexpected challenge: excessive hope. That hope takes different forms in different groups of people, and it alters expectations about gene therapy in ways that can have far-reaching consequences. As a result, some researchers have begun shifting their focus from the machinations of the genetic material and viral delivery systems that make up these therapies to the perspectives of the human beings who will ultimately be affected by their deployment.

"It's crucial at this point to start to explore what patients [and the public] think they need to know and their attitudes toward these therapies because these are therapies that cost millions of dollars to develop," says Olalekan Lee Aiyegbusi, an applied health researcher at the University of Birmingham in England. If people expect too much too quickly, they will end up disappointed or distrustful of the research enterprise; if expectations are too low, not enough people will invest money, time or patient power in the cause.

TROUBLING ASSUMPTIONS

THE TERM "GENE THERAPY" emerged in the public consciousness nearly five decades ago. By fixing defects in our DNA, scientists speculated, gene therapy had the potential to undo thousands of inherited conditions. When gene therapy comes up in conversation, however, some people's thoughts slide from treating disease to engineering human traits such as eye color, IQ and athletic ability—a concept referred to as genetic enhancement. That association, researchers say, is not only inaccurate but harmful.

Speculation about such Gattaca-like futures swelled in 2018 after the Chinese scientist He Jiankui announced that he had created the world's first gene-edited babies by removing copies of a gene in embryos before they were implanted. He was convicted of "illegal medical practice" and sentenced to three years in prison, and scientists around the globe have called for a moratorium on genetic edits that could be passed on to future generations. Experts say that conflating such morally fuzzy research with studies focused on treating disease could derail the conversations that need to take place around the more pressing applications of gene therapy.

Photograph by Sylvia Jarrus

Melissa Creary, pictured here near her home in Ann Arbor, Mich., has seen sickle cell disease from both the academic and the patient perspectives.

Juliette Delhove, a gene therapy researcher at the University of Adelaide in Australia, has examined dozens of studies of public opinion and attitudes toward gene therapy and gene editing. In 2020 she published a scientific review showing that people's support can shift depending on how gene therapy is defined. There is substantially less support for enhancement technologies—which one person likened to "playing God" and another criticized as "going against nature"—than there is for therapies for serious or fatal diseases. In one study, only 35 percent of respondents believed it was definitely acceptable to use gene therapy to enhance memory, compared with 93 percent who supported its use to treat an inherited form of blindness known as Leber congenital amaurosis.

Delhove and others have found that people bring their life experiences to conversations about the technology, and such experiences shape their perspectives. Studies show that people with more education and some knowledge of genetics are generally more accepting of gene therapy, whereas those with strong religious ties tend to be less accepting, even when it is used to treat cancer or prevent blindness. But perhaps the biggest factor in how someone views gene therapy is whether they or someone they love is affected by a disease the innovation aims to cure. Ultimately, says Holly Peay, a social scientist and genetic counselor at the nonprofit RTI International, "a lot of what we're seeing in the literature that exists are people's emotional reactions."

"We are, as a species, wildly optimistic about ourselves."

—*Holly Peay,* RTI International

THE RISKS OF HOPE

TALKING ABOUT GENE THERAPY can seem like a hypothetical exercise—for someone without anything at stake, it is a chance to explore technological progress or debate ethical principles. But for patients, such discussions have real-life implications. Every new data point is a signal that they might be just steps away from overcoming their illness. When Creary thinks about gene therapy, she considers its potential impact on her daily life. "There's a scientific innovation that will take the pain away," she says. "That is the crux of the hope conversation: I could live a day without pain."

Creary has been wary about giving herself over to that hope, but patients generally tend toward enthusiasm, often holding unrealistic expectations of benefits from treatments that have not yet proved effective in clinical trials. Researchers have a name for this: therapeutic optimism. "We are, as a species, wildly optimistic about ourselves," says Peay, who works with patients and families with the progressive muscle disorder Duchenne muscular dystrophy. Repeatedly she has heard patients share their hopes that a clinical trial will heal them, even after they have read extensive informed consent forms and heard investigators explain that they are just as likely to receive no benefit. Peay thinks that optimism is not necessarily a bad thing. "People need hope," she says. "Hope is important. Therapeutic optimism is an expression of hopefulness."

The problem starts when people fail to recognize that a clinical trial is an experiment, not a treatment. Researchers have named this phenomenon, too: therapeutic misconception. They describe it as a blurring of the lines—an inability to distinguish between an approved treatment chosen and dosed specifically for a patient and a trial designed to further the science. "It's kind of a perfect storm of the natural optimism and expectation of people who are desperate and clinical investigators who are, honestly, hyping their trials," Peay says. She spends a lot of time trying to rectify mismatched expectations, which often arise in those facing rare diseases with unmet medical needs. According to unpublished research by bioethicist Jonathan Kimmelman of McGill University, only about one in 70 people in a phase 1 clinical trial will receive a drug at a dose that will ultimately receive FDA approval, whereas up to 15 percent of participants could experience a severe side effect.

Setbacks during the early iterations of gene therapy [see "Overcoming Gene Therapy's Long Shadow," page S8] showed scientists how much more they needed to learn about the underlying biology. Research has since filled in critical knowledge gaps, resulting in several FDA-approved gene therapies and dozens more likely to be approved by 2030.

Remarkable successes could lead some people to believe the field is moving faster than it really is, warns Rachel Bailey, a gene therapy researcher at the University of Texas Southwestern Medical Center. She points to one treatment, for a fatal neurodegenerative condition called Batten disease, that moved from concept to human testing in a little more than a year. Gene therapy has slowed the progression of Batten disease, but "at this point," Bailey says, "we're not at the cure stage yet. We are at the treatment stage." A true cure will take much more research. "I think what's important for patients to understand is that it takes a very large amount of time, effort and funding to develop these gene therapy products," Bailey says.

QUESTIONS OF EQUITY

GENE THERAPY'S RISE TO PROMINENCE has come with an extraordinarily high price tag. Novartis's newly approved gene therapy, a one-time treatment for spinal muscular atrophy, is now the world's most expensive drug at $2.1 million. On average, currently available gene therapies are priced at more than 30 times the average household income. "We must be thinking right now about the equity question and how we make sure that as many people as possible benefit from the technology that's built on government funding, that's built on great science," says Vence Bon-

ham, acting deputy director of the National Human Genome Research Institute and leader of the NHGRI Health Disparities Unit.

Bonham has been talking about this issue for a while. In 2017, before the first gene-editing trial for sickle cell disease had been approved, his team interviewed more than 100 patients, families and physicians to gauge their attitudes and beliefs about the technology. Many were hopeful but cautious. "If this treatment becomes available to the public, will it be available to everyone equally?" one patient asked. "I have sickle cell. I struggle with it daily.… I don't want the reason why I can't get it done to be because, oh, your insurance, or you don't have the money."

Cost is not the only concern. In the U.S., only about one in four people with sickle cell disease receives the standard of care. These patients can be marginalized and dismissed, often having to wait longer for help in the emergency department than other pain patients. Creary herself has spent hours writhing in pain in hospital emergency rooms, misperceived by staff as drug seeking because she is Black and has sickle cell disease. She found a way to get her Ph.D. added to her medical record and learned to code switch, dropping hints about her academic titles in the hopes that health-care staff might equate her, she says, with "acceptable auspices of humanity."

Creary has noticed scientists promoting the narrative of gene therapy as social justice—a way of repairing the damage done to those living with sickle cell disease. She points to the Web site for the NIH's Cure Sickle Cell Initiative, which opens with, "It's time to rewrite the story of sickle cell." The statement seems to suggest that scientific innovation can rewrite history or at least right the wrongs wrought by historical neglect and racism. But Creary, who studies a concept she calls bounded justice, believes any justice achieved by targeting new gene therapies to marginalized populations will inevitably be limited by the very inequities that caused those groups to be marginalized in the first place.

"You let [gene therapy] out into the wild, and then all of these historical, societal and anthropological things are going to muck it up," Creary says. Her research suggests that discussions about gene therapy, at least for sickle cell disease, must address big issues such as colonialism, slavery, racism, and "all the things that come from generations and generations of oppression." Part of that is recognizing that physicians make assumptions about who may or may not be a good candidate for gene therapy. It also involves addressing social supports that could counteract the disadvantages many gene therapy patients face, such as health insurance to cover the procedure, transportation to and from the hospital, child care and paid time off for recovery. "It is tough, I think, because on some level it's this recognition that it's never enough," she says.

DEMOCRATIZING INFORMATION

ONE WAY THAT SCIENTISTS CAN HELP their technologies land equitably in the world, Bonham says, is to center conversations on building trust, providing quality information and ensuring transparency. It is an important triumvirate that will take concerted effort from all involved.

Emily Howell, a science communication expert at the University of Wisconsin–Madison, says that the trust part happens when researchers meet people where they are by asking about their concerns, their hopes and their fears. Howell, who studies how to communicate controversial topics such as fracking and gene editing, says starting with emotions and values rather than with facts and figures can help to foster trust. People tend to trust someone when that person not only is competent but also seems to care about the same things as they do, Howell says.

Clarity of information has been another big obstacle. Patients have had a difficult time finding information that is accurate, actionable and understandable. U.T. Southwestern's Bailey says people with genetic diseases often have little choice but to try to make sense of esoteric research papers on their own or to hunt down scientific experts like her to answer their questions. She chairs the American Society of Gene and Cell Therapy's Patient Outreach Committee, which aims to foster open dialogues and easy access to information with a Web site that breaks down various aspects of gene therapy from a patient's perspective. Delhove concurs and says that accurate information empowers people to make decisions for their own health. "That's what you want for patients," she says. "They shouldn't just be bystanders; they should be in control and know what is available for them."

The last of Bonham's trio—transparency—requires researchers to lay out precisely what is and is not possible and to be open and honest when something goes awry. In 1999 18-year-old Jesse Gelsinger died while participating in a gene therapy trial that he hoped would help others with the same rare liver disorder. In the years since, any safety scare has raised the specter of repeating history. Two gene therapy trials for sickle cell disease were temporarily suspended earlier this year after one of the participants developed cancer (it was later deemed unrelated to the treatment). Bonham says the pause was a clear sign of the scientific community's renewed commitment to engagement and transparency. "I think we've seen a really positive shift occurring with regard to our understanding that gene-based therapies have potential," he says, "but that doesn't mean that they don't have any risks."

Today, after several frank discussions buoyed by her own deep dives into the literature, Creary is well aware of those benefits and risks. She knows gene therapy might completely erase her sickle cell disease, untethering her from its pain and complications. But she has also learned how intense the procedure would be, with punishing rounds of chemotherapy and lengthy hospital stays. "I think about measuring that destabilization in that moment with what I could gain, in addition to the risks, and I'm still not sure," she says.

More than a million people could be eligible for gene therapy in the next 15 years. The conversations researchers have today, both with the general population and with their patients, may ultimately determine how the field evolves. With the right support, it could be revolutionary. Without it, an immeasurable amount of time and treasure will have been spent honing a technology that may never fulfill the hopes of the patients it was designed to help.

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NONFICTION

When the Snow Goes

The far-reaching effects of shrinking winters

Review by Ryan Krogh

With each new report about the impending—and ongoing—effects of climate change, it's easy to catastrophize. In the coming decades, as glaciers around the planet melt and sea levels rise, hundreds of millions of people living in low-lying coastal communities will be forced to relocate to higher ground. But the mountains are no safe space either, as wildfires increase and water becomes scarce—both of which are a result of disappearing snowfall. "Frozen water has made our world," writes author Porter Fox. "And as it vanishes, everything in our backyards, our cities, our homes, our jobs, and our lives is going to change."

For the 670 million people living in high mountain regions worldwide, the shrinking glaciers (as well as the rivers they feed) will leave those once snowy areas without water, parched to the point of geologic dehydration. Within the next three decades the length of winter in the U.S. could decline by 50 percent. A 2004 study in *Climatic Change* predicted a drop in snowpack depth of 25 to 100 percent by the end of this century; another study warns that the Southwest will not have enough snow to support ski operations by 2050. Such dramatic losses will devastate the West's forests and dry up rivers like the mighty Colorado, which supplies water to some 40 million people and has been in drought for more than 20 years. Indeed, the first-ever water-usage cutbacks were applied to its basin states in August.

But what's lost in those reports and the doomsaying that often follows is the creative, persistent people behind the study abstracts: those dedicating their lives (and sometimes risking them in the process) to research in some of the world's most remote and wild places. In *The Last Winter,* Fox puts names and backstories to much of the data as he travels from Washington State to Alaska to Greenland to Switzerland and beyond, connecting with the scientists who are often painstakingly collecting information that the rest of us rely on to make sense of our changing planet.

The Last Winter:
The Scientists, Adventurers, Journeymen, and Mavericks Trying to Save the World
by Porter Fox.
Little, Brown, 2021 ($28)

The book is part adventure travelogue, part profile collection and part essay, as Fox, a lifetime skier, contemplates what the world will be like without snow. Because of this mash-up, *The Last Winter* can feel a bit disjointed at times, and it's occasionally hard to keep tabs on who's who, as Fox leaps from one person to another and from location to location. (It doesn't help that the pandemic interrupted the book's far-flung reporting.) But when he settles into a new character and destination, Fox does an excellent job of humanizing the scientists. In Washington, he goes on a backcountry ski tour with Kelly Gleason, a researcher at Portland State University who helped pioneer the study of a particular feedback loop: when black carbon from burned trees falls onto snow, it absorbs more sunlight, causing the snow to melt faster and dry out the forest earlier, creating more fire-prone forest. The idea had come to her while skiing in a burn scar. When Fox asks Gleason what will life be without winter, she responds: "Yeah, I'm not ready to deal with that."

The writing is at its best when Fox describes the landscapes. In the Arctic, for example, "It never really gets dark.… The reflective surface of the snow and glaciers glows blue under the moon and stars. Night is an afterworld of ghostly shapes and distant sounds, like opening your eyes underwater." He meditates on what the fading of winter will mean for the cultures that rely on it—both the ancient native cultures and modern recreational ones like skiing. In Greenland, Fox embeds with a crew of Inuit guides who seem more prepared to confront the harsh realities of climate change than most.

Still, it's the research on the ongoing losses in the cryosphere that provide the book's heft, if only because of the dire state it portrays. As Fox notes when discussing the multiplying effects of droughts, forest fires, diminished snowpack and longer summers: "As with most in the world of climate change, the problem compounds. Lack of snow cover allows sunlight to sustain new plant life earlier in the spring—adding more demand on the shrinking water supply and more fuel for fires."

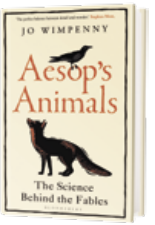
If there are faults to *The Last Winter,* it's that the book suffers from the same shortcomings as much reporting on climate change: it's too focused on the canaries in the coal mine. The rapid pace at which we've already lost glaciers and biodiversity (to name just two examples) haven't yet propelled our species to take up aggressive action. Fox writes with sincerity that "measurement is the key to solving climate change," but it's a wide-eyed view. It's what we do collectively with those data that matters most now, and the book offers few nods toward the type of transformative solutions we need.

Coming away from reading *The Last Winter,* there's no other way to feel but, well, full of dread. As Fox notes, "The sedating effects of modern convenience [make] it seem like everything [is] going to be alright, like someone would figure everything out."

Illustration by London Ladd

ESSAYS

Facts and Fables



Aesop's Animals: The Science behind the Fables
by Jo Wimpenny. Bloomsbury Sigma, 2021 ($28)

Come for the fables and stay for the behavioral research in this jam-packed but delightful collection of essays. Each chapter of *Aesop's Animals* begins with a tale from the mononymous Greek storyteller—"The Ant and the Grasshopper" (*right*), "The Fox and the Crow," plus seven others—and then weighs its plot against centuries of inquiry. Do lions reward acts of altruism, like Aesop's big cat with a thorn in its paw? Are wild wolves capable of deception—sheep's clothing or otherwise? What, exactly, is a crow's grasp of physics? For the answers to such questions, author and animal researcher Jo Wimpenny takes us into the field, the zoo and the lab.

Many animals in Aesop's stories align with the biologies of their flesh-and-blood counterparts. Studies confirm that a dog like the one in "The Dog and Its Shadow" would mistake its own reflection for a rival. But other fables depict animals in ways that contradict science. The asses of Aesop, for example, never display the patient, gentle competence frequently observed in the world's donkey species. And sometimes the answer to whether Aesop got things wrong is trickier. To judge the accuracy of the monkeys that "ape" humans in "The Monkey and the Fisherman," for example, scientists would need to first agree on what imitation even is—a controversy still unresolved despite a century of research and discourse.

Along the way, Wimpenny introduces us to vivid characters—human and otherwise—from the history of animal studies. Take the Progressive Era psychologist who tested primate intelligence by studying a chimpanzee that had been taught to smoke. Or Bertie, the fastest tortoise on record, who was still 70 times slower than the average hare. *Aesop's Animals* is both an intense and playful look at how humans—storytellers and scientists alike—consider the mysteries inside the creatures with whom we share this planet.

—Elena Passarello

AF Fotografie *Alamy Stock Photo*

IN BRIEF

A Natural History of the Future: What the Laws of Biology Tell Us about the Destiny of the Human Species

by Rob Dunn. Basic Books, 2021 ($30)

As we face the effects of climate change, applied ecology professor Rob Dunn cautions against tightening our grip on nature by controlling it with engineering. Instead he urges cooperation with the laws of biological nature that truly govern life on Earth. Dunn's lucid discussion offers insight for surviving climate variability: the law of corridors supports creating habitat bridges to help species flee to new homes; the law of diversity favors growing refuge plants alongside transgenic crops. With the chaos in our future unknowable yet inevitable, Dunn's absorbing analysis advocates making the most of the few certainties we have. *—Dana Dunham*

Super Volcanoes: What They Reveal about Earth and the Worlds Beyond

by Robin George Andrews. W. W. Norton, 2021 ($27.95)

Robin George Andrews acknowledges that volcanoes are often destructive and terrifying. But, he writes, they're also majestic fonts of power that might have been incubators for early life and can teach us much about our own world—and those beyond. As a trained volcanologist, Andrews is in awe of his subjects; his zeal is obvious in his descriptions of each volcano's rocks and lava, which can sometimes verge on overwrought. But his attentive reporting will be enjoyed by both the magma-curious and anyone who just wants to wonder at some of the strangest, strongest forces in the universe.

—Tess Joosse

The Arts of the Microbial World: Fermentation Science in Twentieth-Century Japan

by Victoria Lee. University of Chicago Press, 2021 ($45)

To understand the invisible gardens that give us sake and penicillin, historian Victoria Lee explores the industrialization of Japanese fermentation, shedding light on the " 'microbe smiths' who seek to manage microbial interactions with society." Lee translates a brewing motto, *Onko chishin,* as "find new wisdom through cherishing the old," an apt framing for the book. This porthole into 20th-century Japan is more scholarly than narrative, but there are flashes of intrigue, too: a technician's obsession with precision, the smell of soy sauce supplemented by amino acid, the global transport of two liters of corn steep liquor. *—Maddie Bender*

Naomi Oreskes is a professor of the history of science at Harvard University. She is author of *Why Trust Science?* (Princeton University Press, 2019) and co-author of *Discerning Experts* (University of Chicago, 2019).

IPCC, Your Job Is Partly Done

There's no more need to show that humans are causing climate change

By Naomi Oreskes

In 1988 the International Panel on Climate Change (IPCC) was created as a joint venture between the World Meteorological Organization and the United Nations Environment Program to advise global leaders on the risks of anthropogenic (human-caused) climate change. In 1992 the charge was made more specific, as the U.N. Framework Convention on Climate Change defined the concept of "dangerous anthropogenic interference" (DAI) with the climate system. Scientists were asked to define the level of climate change that would constitute DAI and evaluate what its consequences might be. This past August one of the IPCC's three working groups issued its sixth comprehensive report. One media outlet called it "devastating." Another called it "grim." Crucially, the report confirmed that the current level of warming—just over one degree Celsius—has crossed the DAI threshold.

The report was released during a catastrophic summer of fires and floods during which ordinary observers could see the effects of climate change unfolding in real time, and this no doubt contributed to a high level of media and public interest. But for those of us who have been following the issue, there was little that was really new. Back in 1995 the IPCC had already concluded that the human effect on the climate system was "discernible." In 2001 the panel told us that "abrupt and irreversible" changes could occur. By 2007 warming largely attributable to human causes was "unequivocal," accelerating a measurable loss of mountain glaciers and terrestrial snow cover that was in turn contributing to significant sea-level rise. And there was already strong evidence that warming was exacerbating extreme weather events and that heating and acidification of the oceans were threatening the future of coral reefs and other marine life. The main thing that was new in the latest IPCC report was not so much the science but the tone. In the past, IPCC scientists have bent over backward to be calm and not to overstate the case. But in the latest report, the tone was alarmed. That's good because when the facts are alarming, it is rational both to be alarmed and to convey that alarm to others.

But this raises a question for the IPCC: What now? The answer is for scientists of Working Group 1 to declare their job done and pass the baton to the rest of the scientists who populate the organization. Many people don't realize that the IPCC has three working groups. Working Group 1 (WG1), which issued this summer's statements, addresses the "physical science basis" of climate change. WG2 deals with "impacts, adaptation, and vulnerability," and WG3 looks at mitigation. Put another way, WG2 explores in detail why climate change matters, and WG3 tries to figure out how to stop it. Now that we know that DAI is fully underway, it's time to focus on preventing the problem from getting even worse and figuring out how to adapt to the changes we can no longer prevent. One step that could help that happen would be for the IPCC to declare the job of WG1 to be done and close it down.

After all, if human-made warming is as unequivocal as these scientists insist, then why do we need more reports to tell us the same thing? Closing WG1 would answer that question and would allow climate scientists to refocus on basic science, which is, after all, what most of them are trained to do. And it would encourage public and policy attention to shift to solving the problem. This change in focus will require us to pay closer attention to what our economists, sociologists, urban planners and biologists have to say than we have to date, and these experts are mostly to be found in the IPCC's other two working groups.

Over the past 30 years the physical science that explains the dangers of our interference with the climate system has become ever clearer. Yet our ability to tackle the problem seems to have stood still. When the IPCC first gathered in 1988, the concentration of atmospheric carbon dioxide stood at 352 ppm (parts per million). Today it is 410 ppm and rising. More than half of all emissions have been generated since the IPCC began. Climate change is no longer a question of physical science. So let's thank the climate scientists who have worked so hard to clarify the problem and look to others who can help us figure out how to solve it. SA

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Illustration by Tyra Schad

1971 Fish in Death Valley

"Small springs and streams dot the Death Valley region, one of the most arid deserts. These small aquatic 'islands,' some not much larger than a bathtub, are populated by four species of a tiny fish, known as desert pupfish. More than 20 distinct populations have been identified. Each population is confined to a single, isolated oasis. Some have evidently survived for thousands of years in small habitats where their numbers have never exceeded a few hundred individuals. As a result of evolutionary divergence the species have distinctive shapes and markings."

1971

1921

1871

Underground Nuclear Explosions

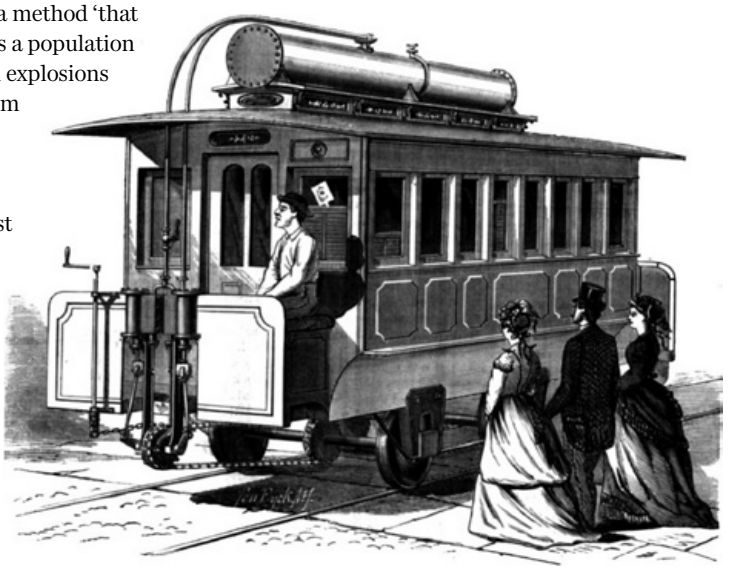
"Since the Limited Test Ban Treaty of 1963 the U.S. has conducted 229 underground nuclear tests and the U.S.S.R. at least 47. These tests have helped seismologists find ways of discriminating between underground explosions and earthquakes, the thorny issue on which efforts to frame a total test ban originally foundered in 1963. A recent article in *Nature* describes a method 'that completely separates a population of [27] underground explosions at … test sites … from a population of [51] shallow … earthquakes … within about 15° of these test sites.' The 27 tests generated seismic signals whose 'body wave' magnitude ranged from 4.2 to 6.2. Body waves, or P waves, travel through the earth's mantle and can be recorded more clearly at distances between 3,000 and 10,000 kilometers from the event than at shorter distances. They are thus well suited for detecting clandestine events."

1921 Edison Tests Executives

"When Thomas A. Edison was trying out candidates for executive positions [at his Menlo Park Laboratory in New Jersey], he set before them a list of 150 questions, none of which had any direct connection with the work. Many scoffed. Enough time has elapsed for the results to have justified this unusual mode of selection. Edison told *Scientific American,* 'It seemed to me that the very first thing an executive must have is a fine memory. Of course it does not follow that a person with a fine memory is necessarily a fine executive. But if he has not the memory, he lacks the first qualification and nothing else matters.'"

1871 Synthetic Speech, Pre-Siri

"The talking machine of Professor Faber is in Philadelphia. In the exhibition last night, phrases of six and eight words were spoken in English, French and German. The voice is a shrill, monotonous and unnatural one, but in the majority of instances startlingly correct, received by the audience with applause. The machine consists of a gilded table, beneath which appears a bellows. Upon the top a lifeless face, with clammy eyes, stares at you, and behind it is arranged a mass of wires, strings, delicate wooden levers, rubber tubes and pipes. Compressing the bellows forces air through an iron windpipe, and thence into an artificial glottis, from which it passes through a vent representing the human mouth, with movable jaws and rubber tongue. Fourteen levers, when moved in concert, produce the sound of any desired syllable. A separate lever causes a peal of laughter."



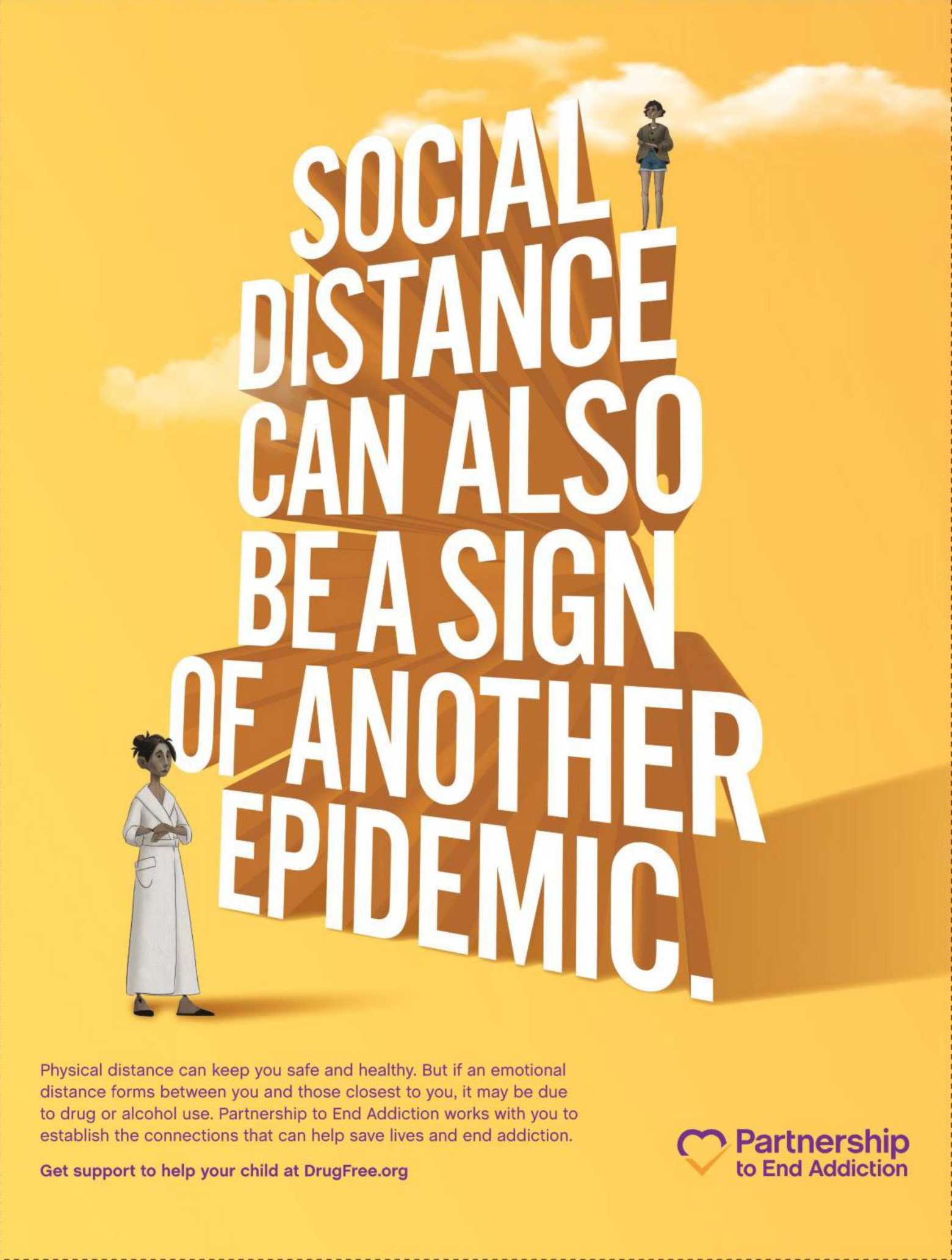
1871: Ammonia streetcar. "Ammonia possesses great theoretical advantages over steam as a motive power, but … the material is much more expensive than water, and … small leaks … act corrosively.… Dr. Emile Lamm, of New Orleans, has attacked the practical difficulties with great success."

Heat Prevents Colds?

"Chills and fever have been attributed for ages to 'miasm,' an emanation from the earth so subtle that the ablest chemist was not able to detect it. But the microscope has discovered in the miasmatic air a multitude of living things. Whether this life is animal or vegetable is in dispute, but it results from warmth, moisture and vegetation combined. To be injurious, it must be breathed into the lungs, or swallowed into the stomach. But cold makes it so heavy that it falls to the earth, and can be neither breathed nor swallowed. Heat carries the miasm towards the clouds. An hour after sunrise until an hour before sunset, as a general rule, it is too high above our heads to injure us because of the heat of the weather. To [be] safe in spring and autumn, dress by a cheerful blazing fire, and take breakfast before going outside. Come home before sundown, take your supper before its setting, by the same cheerful blazing hearth, then go and do what you please."

By the 1880s most physicians subscribed to the germ theory of disease, discarding the miasm idea, touted by Hippocrates in the fourth century B.C.

Scientific American, Vol. XXV, No. 19, November 4, 1871



Physical distance can keep you safe and healthy. But if an emotional distance forms between you and those closest to you, it may be due to drug or alcohol use. Partnership to End Addiction works with you to establish the connections that can help save lives and end addiction.

Get support to help your child at DrugFree.org

Partnership to End Addiction

From discovery through delivery: Patient-focused development of gene therapies for rare diseases

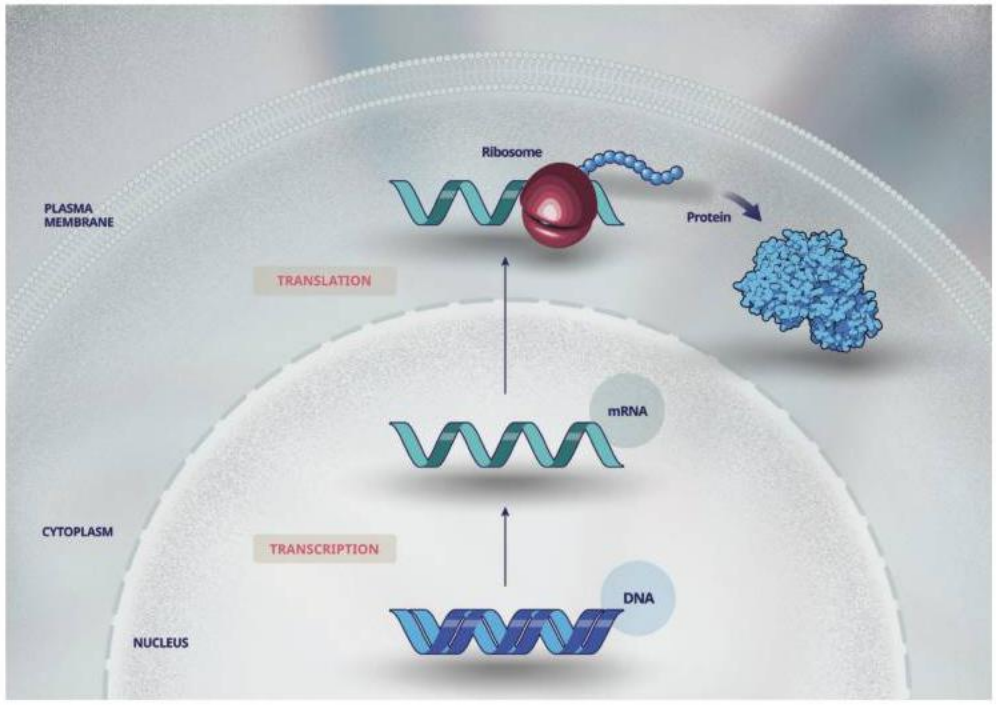


Figure 1. The central dogma of biology. The process in which DNA is transcribed into RNA, which is then translated into protein, is called the 'central dogma' of biology. Proteins can have activity inside the cell in which they are made or travel to other cells and tissues to exert their function. DNA – deoxyribonucleic acid; RNA – ribonucleic acid; ribosome – cellular structure used to translate RNA into protein.

For people living with rare genetic diseases – many of which can be debilitating or life-threatening – the need for innovative treatments is urgent. Only 5% of the 7,000 known rare diseases have an approved treatment, making patients with rare diseases collectively one of the most underserved communities in medicine today. Ultimately, the ability to realize the full potential of gene therapy to treat rare genetic diseases depends on listening to and addressing patients' needs. Pfizer aims to establish a new paradigm; leading the way to bring new medicines to patients with a rare disease by including the patient voice at every stage of innovation and by leveraging the company's expertise in rare disease research to develop a portfolio of potentially transformative recombinant adeno-associated virus (rAAV)-based gene therapies.

"Prioritizing the patient voice is essential as we advance our gene therapy pipeline."
Katherine L Beaverson, senior director, patient advocacy lead, Rare Disease Research Unit at Pfizer.

THE COLLECTIVE GLOBAL IMPACT OF RARE DISEASE

About 80% of rare diseases, defined in the United States as those that affect fewer than 200,000 people and in the European Union as diseases that affect no more than 1 in 2,000 individuals, are due to genetic mutations. Roughly half of all rare diseases predominately affect infants and children and can lead to significant illness and early death. While each genetic disease may occur in a small population of patients, collectively rare diseases affect approximately 400 million people worldwide and are responsible for significant loss of health, life and economic potential. The few treatments that have been available typically have focused on disease symptoms, without correcting the underlying cause of disease.

The symptoms and health impact of rare genetic diseases vary, but most of them result in the loss or alteration of a protein that is needed for cells and organs to function normally. Our genes are encoded in the DNA (deoxyribonucleic acid) of our chromosomes, which reside within the nucleus of the cell (**Fig. 1**) and contain the instructions to make all the proteins that our bodies need to be healthy. DNA is copied (transcribed) into RNA (ribonucleic acid), which leaves the nucleus and delivers these instructions to the protein-making machinery (ribosomes) outside the nucleus.

Genetic disorders result from inherited or spontaneous changes in the DNA code (mutations). These changes can lead to the loss of function or gain in toxic function of a protein and subsequent alteration of cell function. Genetic medicines that restore functional patterns of protein expression hold great promise in treating rare diseases. Treatments include gene therapy (which the American Society of Gene and Cell Therapy defines as the introduction, removal or change in genetic material – specifically DNA or RNA – into the cells of a patient to treat a specific disease, although other sources may use different definitions), gene editing (permanently correcting, stopping or altering the mutation within the patient's own DNA), and gene regulation (altering the transcription of the gene to RNA or translation of RNA to protein).

GENE THERAPY HAS THE POTENTIAL TO ADDRESS THE UNDERLYING CAUSE OF RARE DISEASES

Gene therapy represents the next step in the evolution of therapeutic development, which began with chemical compounds to treat symptoms (for example, aspirin to treat pain) and then advanced to biologic therapies (which could include proteins and antibodies) that modify disease (for example, enzyme replacement therapy to treat some inborn errors of metabolism, such as Gaucher disease). Now, gene therapy offers the potential to address the underlying biology of rare genetic diseases, which could reduce ongoing need for treatment, thus decreasing the treatment burden for patients and reducing health system demands. It may also improve quality of life for caregivers, especially parents, who today face significant emotional, physical and financial challenges. Enabling patients to live longer, healthier and more productive lives may further increase their ability to make positive contributions to their societies and economies.

"Gene therapy may seem straightforward in principle, but it's scientifically complex in practice."

Abhi Gupta, senior director, Global Gene Therapy Business at Pfizer.

INNOVATION IS ESSENTIAL FOR REALIZING THE PROMISE OF GENE THERAPY

Our bodies have multiple systems in place to keep foreign substances and DNA out of our cells. Safely and effectively transferring healthy genes to cells (**Fig. 2**) requires delivery methods that can bypass these systems and enable expression of the healthy gene for long periods of time in the specific cells affected by the disease.

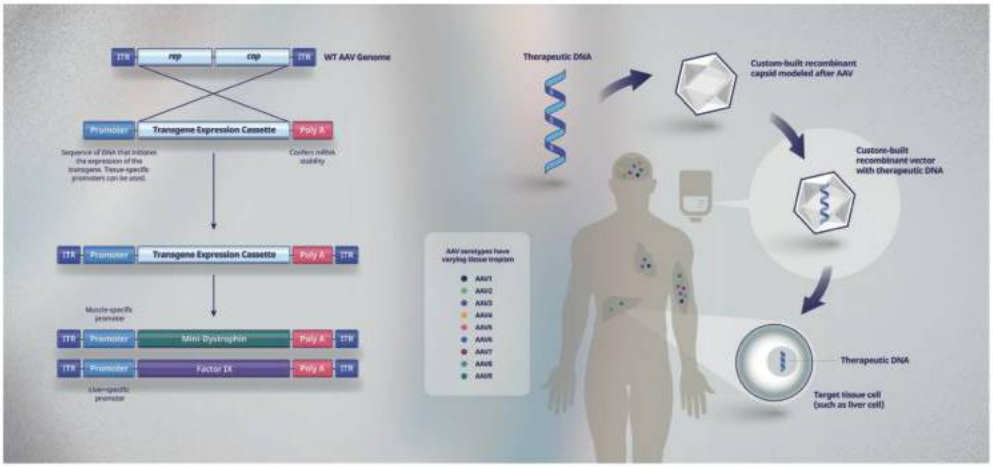


Figure 2. From gene to protein using *in vivo* rAAV gene therapy. The *rep* and *cap* genes are removed from the wildtype (WT) adeno-associated virus (AAV) genome and replaced with an expression cassette that includes the therapeutic transgene, the promoter sequences needed to turn the gene on in targeted cell types, and a Poly A sequence that confers mRNA stability. Gene therapy for Duchenne muscular dystrophy and haemophilia B use transgenes encoding mini-dystrophin and factor IX, respectively. These therapeutic DNAs are then combined with an rAAV capsid to create an rAAV vector that is delivered to the patient by infusion or injection, depending on the target tissue. ITR – inverted terminal repeat of the wildtype AAV genome, which allows transgene replication during the manufacturing process.

Turning a harmless virus into a robust vehicle for gene therapy

Adeno-associated viruses (AAV) can be engineered so that the virus' own genome is replaced with DNA that contains the functioning copy of the gene (known as a transgene) and a switch to turn the gene on in specific types of cells needed to treat a particular disease (known as a promoter). This combination of engineered DNA inside the AAV shell (the capsid) is called a vector (**Fig. 2**).

Engineered recombinant AAV vectors are the most common delivery system in current investigational gene therapy clinical trials, for several reasons. From a safety perspective, AAV is not known to cause disease in humans and it cannot make copies of itself without help from other viruses. This means that rAAV vectors cannot replicate in the human body. The healthy gene delivered by the rAAV vector also predominantly remains separate from the patient's own DNA, which helps prevent generating additional mutations that might potentially occur if it were to be inserted into certain locations in the patient's chromosomes. rAAV vectors have the potential to provide long-term expression of the healthy gene, and multiple strains of AAV (known as serotypes) enable development of rAAV vectors designed to preferentially target the cells needed to treat a particular disease (**Fig. 2**). Additionally, rAAV vectors can be delivered directly to the patient by infusion or injection (known as *in vivo* gene therapy). Importantly, rAAV vectors are already being utilized in gene therapies approved for use in the United States and Europe, demonstrating their viability. For all these reasons, Pfizer uses rAAV vectors for *in vivo* gene therapy as its main approach to rare disease gene therapy.

PFIZER'S END-TO-END rAAV GENE THERAPY PLATFORM

Pfizer has established what we believe to be an industry-leading end-to-end (discovery, through development and delivery) gene therapy platform to help realize the potential of gene therapy in treating a variety of rare genetic disorders and ensure that patients' needs and perspectives are considered at every stage of development (**Fig. 3**). This end-to-end platform leverages Pfizer's extensive rare disease drug development expertise to advance gene therapy development timelines, support global gene therapy trials, and engage early with patients to understand their needs. This approach has enabled one of the largest pipelines of Phase 3 gene therapy programmes in the industry (haemophilia A, haemophilia B, and Duchenne muscular dystrophy) and multiple preclinical programmes in rare haematology, neurology, cardiology and endocrine/metabolic diseases.

Discover

In the discovery phase, Pfizer scientists evaluate the part that specific gene mutations play in disease. Then they determine the best way to deliver a healthy copy of the gene to the right cells in order to treat the disease. They also determine if there is an age or stage of disease before or

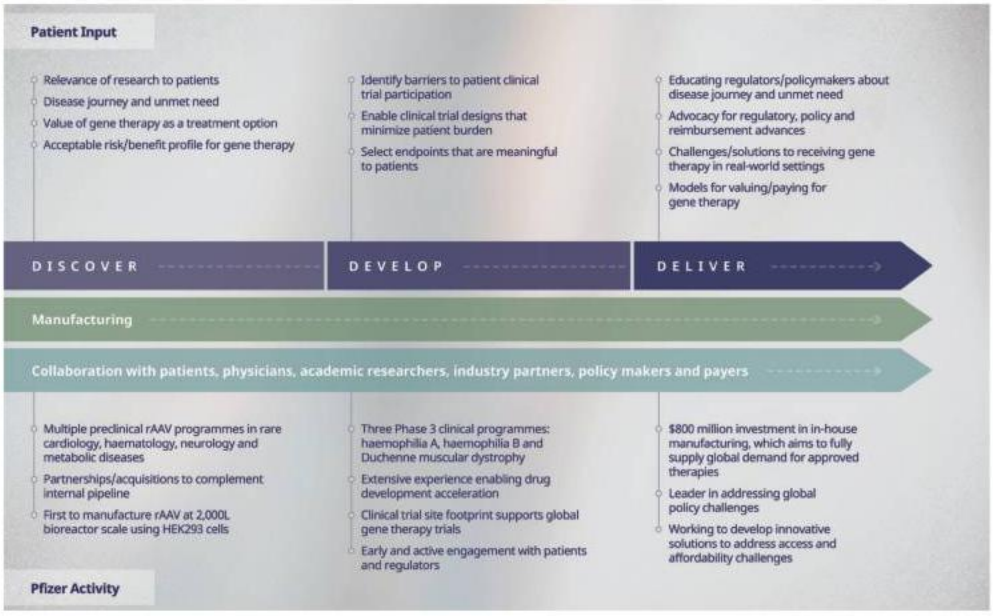


Figure 3. Pfizer's end-to-end, patient-centric approach to gene therapy development. Pfizer's approach to gene therapy spans discovery, development and delivery. Patient engagement by stage; Pfizer activity by stage; manufacturing and collaboration are critical end-to-end.

after which gene therapy is not as likely to be effective. For example, Duchenne muscular dystrophy presents early, progresses rapidly and leads to muscle damage and failure over time. In this and other progressive diseases, gene therapy may prevent significant and irreversible damage when administered in childhood and may prevent further decline when administered to older patients.

A variety of activities happen during the development phase, including conducting clinical trials that prioritize the safety of participating patients and provide the safety and efficacy data that patients, physicians, regulatory authorities and other stakeholders need to make informed approval and treatment decisions. Several important considerations go into designing trials that achieve these goals. One consideration is determining which patients are most likely to benefit from the gene therapy being tested, which, as noted above, may depend on a number of factors. Another consideration is the approach to patients who may already have antibodies against AAV. Because AAV is a naturally occurring virus, many people have already been exposed to it, and their immune systems have been primed to prevent AAV (and related rAAV vectors) from entering cells. Some of these antibodies can keep rAAV vectors out of cells (known as neutralizing antibodies, or NAbs). Significant levels of NAbs may block the rAAV gene therapy from getting into enough cells to have a therapeutic effect. For this reason, many rAAV clinical trials currently exclude patients who have levels of NAbs above a certain value. From a safety standpoint, the immune response to AAV can potentially lead to adverse effects related to rAAV vectors. To reduce this risk, rAAV gene therapy clinical trials often include temporary use of medications that reduce the host immune response and have processes in place to monitor and respond to these events if they arise.

The assessment of whether a potential therapy provides benefit is determined by measuring changes in specific clinical trial assessments, known as endpoints. Endpoints can include changes in levels of the therapeutic protein produced by the delivered gene (for example, Factor VIII or Factor IX for haemophilia A and B, respectively, or mini-dystrophin for Duchenne muscular dystrophy), changes in physical functions such as walking speed or ability to climb stairs (Duchenne muscular dystrophy), bleeding rates in haemophilia and the patients' own perspectives on how life with their disease has changed in response to the treatment. Choosing endpoints that matter to patients and that can be measured consistently and reproducibly may be challenging, especially for diseases in which consensus on how to define 'benefit' has not yet been reached. Therefore, consulting with patients, clinicians and regulators is essential for selecting endpoints that are meaningful to patients, can be used consistently in clinical practice, and provide regulators the information they need to evaluate and potentially approve a new therapy. Finally, creating registries that collect long-term data from patients who receive new gene therapies, once they are approved, is important for the continued evaluation of safety and efficacy over many years.

Develop

The development phase also includes working with regulators to establish a path towards potential product approval that balances the need for robust safety and efficacy data with the often-urgent unmet need for a new therapy. This is a complex process that necessitates effective collaboration among regulatory agencies, patients, patient advocacy groups, industry and academia. A comprehensive regulatory strategy also needs to reflect the priorities and processes of different global regulatory agencies. As a company with a legacy of more than 170 years of success in discovering, developing and delivering therapies to patients around the globe, Pfizer is leveraging its regulatory expertise to support its rare disease gene therapy pipeline. It is also engaged in collaborative efforts to harmonize regulatory requirements across different countries and regions to streamline the approval of rare disease gene therapies and ensure access to approved therapies as quickly and broadly as possible.

Deliver

The delivery phase comprises activities designed to ensure that approved gene therapies reach the patients who may benefit from them. This includes innovative work with payers and policy makers to develop novel solutions that ensure patient access to potentially one-and-done therapies that may provide benefit for many years or over a patient's lifetime. Managing supply chain logistics and educating healthcare practitioners are critical for facilitating delivery of gene therapies to patients' community care settings and sparing patients from the burden

of travelling long distances to specialized treatment centres. Expanding access to genetic testing to enable early diagnosis of a rare genetic disease is also important for the delivery of gene therapies. This is especially true for rapidly progressive diseases in which early treatment may provide the greatest benefit.

Throughout discovery, development and delivery, Pfizer proactively engages with patients. During the discovery phase, patient insights illuminate scientists' understanding about how rare genetic diseases impact their daily lives, what types of changes or improvements in their disease symptoms would be most meaningful to them, and what risks they are willing to accept or not accept to achieve those changes. Throughout clinical and regulatory development, patient input can help optimize clinical trial designs by identifying barriers to participation and identifying what measurements are considered meaningful and should be used to determine that a new therapy is effective. Patients also have an important part to play in ensuring that approved therapies can be readily delivered, by helping to educate regulators, policymakers, and payers about their needs and the potential value that a new therapy may provide to them and their caregivers.

"Scalable processes ensure a high-quality product regardless of the amount produced."

Patrick Bastek, executive director, Medicinal Sciences, Rare Disease Category Leader at Pfizer.

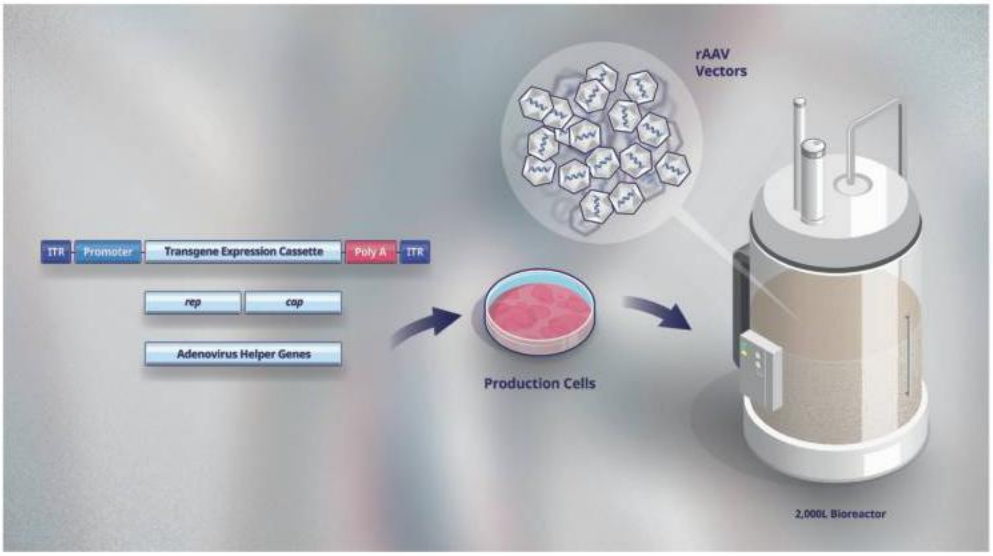


Figure 4. Components of Pfizer's rAAV triple transfection manufacturing process. Pfizer's process to manufacture each of its rAAV gene therapy candidates requires a production cell line and three different components (known as triple transfection): the genetic material (transgene) to be carried by the vector, key replication and structural proteins for the vector (*rep* and *cap*), and other (helper) proteins that aid the replication and assembly process. All three components are introduced into a production cell line (such as HEK293 or other established cell line). The transfected cells are cultured in bioreactors, where rAAV vector production takes place.

MANUFACTURING EXCELLENCE SUPPORTS SUCCESS

Clinical trials of investigational rare disease therapies often include smaller numbers of patients than those for larger disease indications, which may result in compressed clinical development timelines. Therefore, the manufacturing processes for these therapies need to be established and approved on an often shorter timeline than other types of therapies. This may lead to regulators having more questions about gene therapy manufacturing practices than with other types of drugs in development. The regulatory landscape for gene therapy manufacturing is also complicated by the fact that many aspects of the key regulatory requirements continue to be refined. Moreover, manufacturing requirements may differ among regulatory agencies, which adds complexity when trying to make these novel therapies, if approved, broadly available around the world.

Like the manufacture of other biologics, the first step in this process is developing what is known as a production cell line (**Fig. 4**). The production cells act as mini factories that make the rAAV vector. Once the production cell line has been created, the cells are grown in culture and transfected to produce trillions of rAAV vectors, depending on the disease indication. The number of rAAV vectors needed to treat a tissue such as muscle, which is located throughout the body, is tens of thousands of times greater than the number needed to treat, for example, retinal diseases for which the rAAV vectors can be injected directly into the retina.

Pfizer uses large vessels (also known as bioreactors, **Fig. 4**) like those used to manufacture the company's other biologic therapies. The production cells must be lysed to release rAAV vectors into the growth medium in which the cells are growing. The liquid is collected and treated in several steps to remove any cellular debris or other manufacturing byproducts or impurities. Additional steps are also used to reduce the number of 'empty' vectors that do not contain the healthy gene. These multiple purification steps, each of which includes quality control tests, result in a high-quality rAAV vector product, which is then packaged for cold shipment and delivery. Manufacturing demands increase as a gene therapy candidate moves from the discovery stage through clinical trials, and approved gene therapy products which will require sustained production capable of meeting global patient demand.

The expertise in packaging and cold supply chain management that Pfizer developed in support of its gene therapy pipeline played a critical role in its ability to rapidly develop and deploy a cold chain process for delivering the Pfizer-BioNTech COVID-19 vaccine around the world. Additional insights gained from the deployment of the vaccine are being incorporated into innovative cold chain management processes for its gene therapy candidates. Processes that go beyond approaches traditionally

used for biologic therapies are expected to enable more efficient delivery of rAAV gene therapies, if approved.

Pfizer's end-to-end rAAV manufacturing process builds on the company's expertise in manufacturing other biologic therapies, to produce high-quality vectors that can be scaled to meet development stage and dosing requirements of its gene therapy candidates. This expertise is critical for preventing regulatory delays as gene therapy candidates move from clinical trial development to global delivery, and across a wide range of doses. The company has established a diversified manufacturing infrastructure to support end-to-end development through future delivery of its gene therapy candidates, which includes cutting-edge manufacturing facilities in Morrisville, Durham, and Sanford North Carolina in the United States. Combined, these facilities provide Good Laboratory Practice grade material at small scales (10-250 litres) for research and development activities and Good Manufacturing Practice grade material at a variety of scales for early (500 litres) and pivotal clinical (2,000 litres) trials and to ultimately meet global patient demand. The number of doses produced at each scale depends on the disease indication.

PFIZER'S PATH TO REALIZING THE POTENTIAL OF rAAV GENE THERAPY FOR RARE DISEASES

Pfizer is engaged in multiple internal and collaborative efforts to support the advancement of gene therapies.

Advancing science

Scientists are innovating novel rAAV vectors that may more effectively enter target cells and/or make larger amounts of the healthy protein these vectors encode. Researchers are also exploring multiple approaches for reducing potential immune responses to rAAV vectors, which is important for improving safety and efficacy when patients receive a first dose, and for potentially enabling patients to receive additional doses in the future if needed. One of these approaches is plasmapheresis, in which the patient's blood is processed through an external device to remove NAbs prior to the administration of rAAV gene therapy. This is expected to prevent the immune system from blocking entry of the rAAV vectors into target cells. Another approach is to administer medications that temporarily block the immune system from making new antibodies against rAAV vectors. This could also increase the number of rAAV vectors that reach their target cells during initial dosing while blocking the development of antibodies that might reduce the efficiency of future doses, if needed. The temporary use of medications currently used to reduce the levels of antibodies, including NAbs, in some transplant patients may also provide benefit in reducing antibody responses to rAAV vectors in gene therapy patients.

> "Pfizer is committed to innovating ways to address immune-related challenges of gene therapy."
>
> Seng H Cheng, senior vice president and chief scientific officer, Rare Disease at Pfizer.

The availability of these interventions may allow for inclusion of patients who could otherwise be excluded from gene therapy because of high levels of pre-existing NAbs to the AAV vectors. Moreover, while data from approved and investigational rAAV gene therapies demonstrate promising durability of therapeutic protein expression and thereby the potential as one-time therapies, second or even third doses may theoretically be needed in some diseases or for some patients. Pfizer is exploring multiple ways, including the use of combination interventions, to reduce immune responses to rAAV vectors, which is essential for supporting long-term expression from initial doses and enabling re-dosing if necessary.

> "Transforming the hope of gene therapy into reality requires policy innovation as well."
>
> Safiyya Gassman, director, Public Affairs & Policy, Rare Disease at Pfizer.

Expanding global regulatory capacity

The current pace of gene therapy approvals is slower than expected, in many cases due to regulatory complexities. Reducing regulatory delays requires the development and implementation of consistent and standard guidance on clinical trial design and endpoints and clarity for guidance on the chemistry, manufacturing and controls used to produce gene therapies. Ensuring that new gene therapies are available to patients around the world also requires global integration and harmonization of regulatory guidance, and early and productive communication between regulators and gene therapy researchers. Pfizer is leveraging its global regulatory expertise and collaborating with scientific organizations, industry, regulators and others around the world to address the regulatory challenges facing gene therapy.

Developing innovative access models

Traditional therapies for rare genetic diseases are used throughout a patient's life, and current reimbursement policies and payment models are not designed to accommodate gene therapies that may be dosed only once or a few times. Pfizer is working with governments and payers to develop innovative policies and access models that recognize the potential health, economic and societal benefits that gene therapies can provide over a patient's lifetime, and to reduce financial and other barriers to accessing potentially transformative therapy.

The potential of rAAV vectors in enabling new transformational therapies for patients living with rare diseases has been validated. Fully realizing that potential requires continued advancement and innovation across the entire discovery, development and delivery continuum among all stakeholders.

For more information on Pfizer's rare disease therapy portfolio, please visit https://www.pfizer.com/science/rare-diseases/; information on Pfizer's gene therapy programmes is available at https://www.pfizer.com/science/research-development/gene-therapy.

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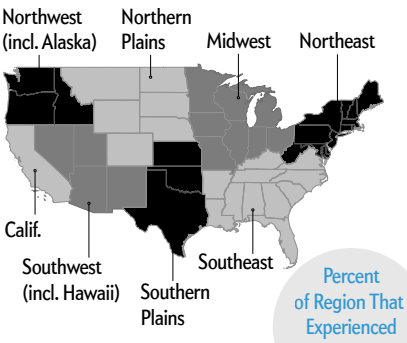
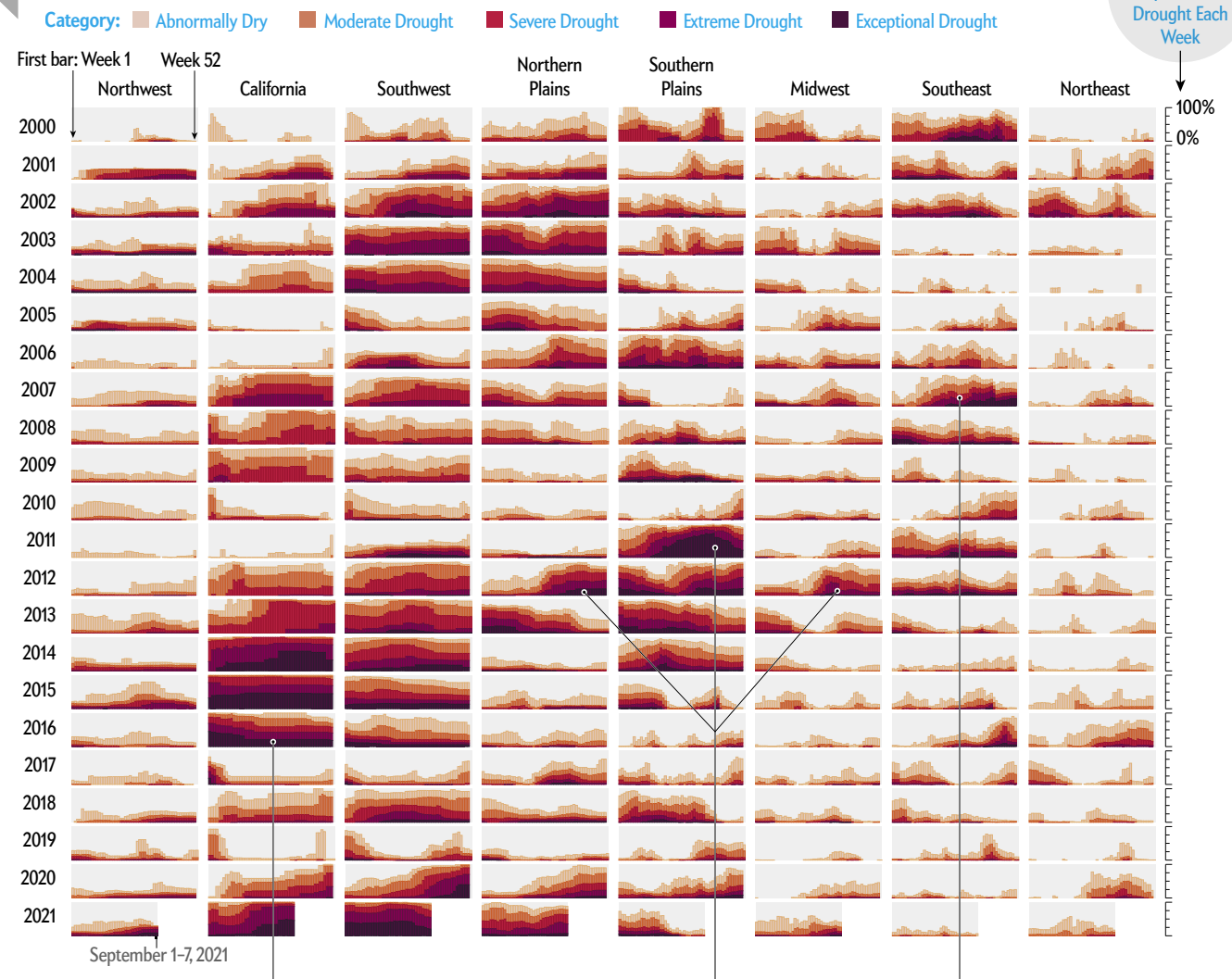
Escalating Drought

Climate change is intensifying periods of extreme dryness, particularly in the U.S. West

For more than 20 years the National Drought Mitigation Center (NDMC) has been monitoring dozens of indices of drought around the country, including satellite measurements of evaporation and color in vegetation, soil-moisture sensors, rainfall estimates, and river and streamflow levels. Although the agency's weekly assessments have identified periods of exceptional drought before, lately dryness has been ramping up. "The changing climate is definitely contributing to more natural disasters, drought being one of them," says Brian Fuchs, a climatologist who oversees the weekly report at the NDMC. "We're seeing more frequent and high-intensity episodes. This year some of these areas in the West have been in drought more than they have been without drought."



Drought Extent and Intensity by Region over Time



California experienced its hottest drought in recorded history from 2012 to 2016. A warming climate makes the atmosphere thirstier, which increases evaporation and boosts drought.

A drought that originated in the Southern Plains in 2011 eventually spread to the Midwest and Northern Plains when the moisture coming in from the Gulf of Mexico was absorbed by the parched South before it could reach the North.

The Southeast's driest year to date was 2007, when only 31.85 inches of rain fell in Atlanta, 62 percent of its average yearly rainfall.

Source: U.S. Drought Monitor, jointly produced by the National Drought Mitigation Center at the University of Nebraska-Lincoln, U.S. Department of Agriculture, and National Oceanic and Atmospheric Administration (*data*)

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The Silent Extinction

Giraffe populations have declined **40%** in the last 30 years.

Our mission is to save giraffes from extinction so they can live freely and safely in the woodlands and savannas of their native Africa.

SAVE GIRAFFES NOW

DONATE NOW!

100% of your donation goes to the on-the-ground projects in Africa to help save giraffe from extinction.

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Photo by Guadalupe Laiz